Pneumonia Before Antibiotics

Therapeutic Evolution and Evaluation in Twentieth-Century America

Scott H. Podolsky

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SCOTT H. PODOLSKY

The Johns Hopkins University Press
Baltimore

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Printed in the United States of America on acid-free paper
2 4 6 8 9 7 5 3 1

The Johns Hopkins University Press
2715 North Charles Street
Baltimore, Maryland 21218-4363
www.press.jhu.edu

Library of Congress Cataloging-in-Publication Data
Podolsky, Scott H.
Pneumonia before antibiotics : therapeutic evolution and evaluation in twentieth-century America / Scott H. Podolsky.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-8018-8327-X (hardcover : alk. paper)
1. Pneumonia, Pneumococcal—United States—History—20th century. 2. Pneumonia, Pneumococcal—Treatment—United States—History—20th century. 3. Pneumonia, Pneumococcal—Chemotherapy—United States—History—20th century. 4. Serotherapy—United States—History—20th century. I. Title.
[DNLM. 1. Pneumonia, Pneumococcal—history—United States. 2. Drug Therapy—history—United States. 3. History, 20th century—United States. 4. Immunization, Passive—history—United States. 5. Pneumonia, Pneumococcal—therapy—United States. WC 204 P742p 2006]
RC771.P72 2006 362.196'241—dc22

A catalog record for this book is available from the British Library.

For Josh and Danny

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Beyond having a substantial impact on my clinical practice and thinking, researching and writing the history of medicine is simply fun (to echo Sherwin Nuland). Being able to thank those who have made this possible is perhaps even more fun.

I have been fortunate to have had mentors who have challenged me at the same time that they permitted me the freedom to dive in and challenge myself. Fred Tauber first supported my over-enthusiastic tendencies with respect to the history of science and medicine and continues to see through the trees and enable me to focus on the most pertinent questions at hand. Allan Brandt has shown me how to approach medicine as inherently social and has served as a role model as both teacher and historian.

Two colleagues in particular—Jeremy Greene and David Jones—not only further taught me how to teach, but provided crucial feedback on the project throughout its development. In addition to my mentors and colleagues named above, Stephen Kandel, Calvin Kunin, Jennifer Rochow, and Peter Tishler worked their way through the entire manuscript, offering both insights and corrections. Jack Lesch and Nick Rasmussen generously read and commented on particular chapters. Wolfram Goessling provided expert assistance with the nineteenth-century German literature. Harry Marks provided the opportunity to present my work at Johns Hopkins, and I am grateful for the feedback provided by him and Ed Mormon, in particular. I have always thought of this manuscript as continuing a dialogue started by two Harry's—Dowling and Marks—and inspired by their efforts and aided by their leads, I can only hope to have approached the rigor of their own work.

One of the great joys I have been exposed to has been that of the translocative experience of intense archival research. I am particularly grateful to the staffs of the Countway Medical Library here at Harvard (and its Center for the History of

Medicine), the American Philosophical Society, the Rockefeller Archive Center, and the University of Pittsburgh for their facilitation of such an experience. The Countway's extensive open stack holdings merit special mention in their own right; there is no way this project could have developed as it did without the serendipity and ease of broad research thus afforded, and the faintly musty smell of "L2" will always trigger the expectant thrill of encountering something new and exciting.

There is also no way this project could have developed without generous financial support. Marshall Wolf, Jane Sillman, and the Brigham and Women's Hospital Internal Medicine Residency Program provided me with the critical first six months of support to get things off the ground. Ever since my post-residency arrival at Massachusetts General Hospital, Michael Barry has generously supported my activities and interests, both through the Division of General Medicine and, along with John Goodson and Susan Edgman-Levitan, through MGH's John D. Stoeckle Center for Primary Care Innovation. The National Library of Medicine provided a publications grant [1 G13 LM 07271-01], which was crucial to supporting the time and archival investigations necessary for the manuscript's completion.

Both formally and informally, my medical colleagues (physicians, nurses, and staff) at the Massachusetts General Medical Group—led by Steve Levisohn—have supported these efforts over the course of five years, and I am grateful for their encouragement and enthusiasm. I am equally grateful to my patients, who not only directly and continually inquired about "the book," but who, of course, further inspired much of my thinking itself.

Jacqueline Wehmueller, at the Johns Hopkins University Press, has provided wise and measured guidance and greatly enhanced the final manuscript. I am likewise grateful to the anonymous reviewer for insightful comments and criticisms, to copyeditor Elizabeth Yoder, and to production editor Carol Zimmerman. Of course, any errors that remain are mine alone.

Last but not least, I could not have written this book without the support of my family. The Fink/MacWright clan (led by my irrepressible grandparents, Roz and Leon), Lois and Jimmy McGuire, Alison and Alan Doe, Jeff Shapiro, Michele and Howard Miron, and Mark Saadeh have been a constant source of encouragement. Lorna and Jack Podolsky's impact on my efforts continues to this day. Judy and Don Shapiro, in addition to providing provocative title suggestions, have provided limitless enthusiasm throughout; I only wish Don could have seen the final product. My parents, Ellen and Steve Podolsky, have provided a lifetime of love, support, and education in all its forms. Finally, I thank my wife, Amy, for her boundless love and the countless ways she has made this book possible. I have dedicated it to our children, Josh and Danny, and thank them simply for being the joys that they are.

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Patterns of Resistance

In September of 1937—two years after the introduction of Prontosil and sulfanilamide, the first of the sulfa drugs—a close relative of John D. Rockefeller Jr. was admitted to the exclusive Phillips House of the Massachusetts General Hospital with pneumococcal pneumonia. The patient's physicians called in experts from the Rockefeller Institute and Boston City Hospital to determine the serological "type" of pneumococcus responsible for the illness, which they accomplished by directly examining the sputum, after processing it with diagnostic rabbit serum. These experts then administered to a Rockefeller himself the embodiment of "scientific" medicine: type-specific therapeutic antipneumococcal antiserum. Developed nearly a quarter-century earlier under Rufus Cole at the Hospital of the Rockefeller Institute, it had been studied and promulgated for use in the large hospitals of the Northeast for over a decade by Boston City Hospital's Maxwell Finland, among others.

Never mind that Max Finland was traveling in Europe at the time, that the patient was already recovering when the serum was administered, or that the treatment itself proved nearly fatal in this instance.[1] By late 1937, antipneumococcal antiserum was not for use only by Rockefellers; rather it had become the focus of federal efforts to transform pneumonia into a national public health emergency, mandating that the public, their physicians, and the public health apparatus unite to provide patients with the wonders of this modern antimicrobial therapy. In December of that year, *A New Day,* a twelve-minute film dramatizing the wonders of antipneumococcal serotherapy that had been jointly produced by the Metropolitan Life Insurance Company and the United States Public Health Service, debuted at Radio City Music Hall and was seen by an estimated 121,000 people in its first week of release.[2] Starring Gilbert Emery as Dr. Mason—who successfully diagnoses an ailing mother's type I pneumococcal pneumonia and saves her at home through the use of antiserum while helping her son to name the family dog in the span of the showing—the film was ultimately shown to more than 17 mil-

lion people at 65,000 presentations nationwide.[3] By that time, Surgeon General Thomas Parran, who had coordinated one of the first "pneumonia control programs" in the country in his previous role as New York State's commissioner of health, had elevated pneumonia to nearly as pressing a public health issue as venereal disease and tuberculosis. In particular, Parran attempted to make centralized "typing" facilities and serum distribution centers accessible to the nation's general practitioners at large so they could treat patients in any location—home or hospital—as early in the course of the disease as possible.

By 1939, when *A New Day* was revised, sulfapyridine, the first of the truly antipneumococcal sulfa drugs, had been released for general sale in the United States. Yet in the revised film, serotherapy continued to share equal billing with the novel chemotherapeutic agent.[4] This was characteristic of the heterogeneous transition (in certain locations rapid, in others, dramatically slow) from antipneumococcal antiserum to chemotherapy that would take place over the next several years in the United States, a therapeutic transformation mediated by the inertia of the profession and the public health system, the needs of general practitioners and their patients, the emergence of a clinical trials ethos, and the influence of a growing pharmaceutical marketing apparatus. By the end of World War II, however, antipneumococcal serotherapy had been displaced; and not only would the immunologically specific therapy quickly be forgotten in the wake of the antibiotic "revolution," but pneumonia's status as a public health concern would be shed as well.

By focusing on the treatment of pneumococcal pneumonia from the 1890s through the 1940s, in particular with antiserum, I thus intend to expand what may start as a narrow aperture into the history of this largely forgotten therapy into a window through which to view the history of therapeutic "specifics"—universally applicable remedies against localizable disease entities—in twentieth-century American medicine.[5] Antipneumococcal antiserum's fascinating and largely forgotten rise and fall sheds historical light on the emergence of modern rational specifics in American medicine, the persistent difficulties in evaluating their efficacy, the continually contentious boundaries between private and public health in their application, and the nature—and implications—of the so-called revolutions claimed in their names.

Perhaps nowhere in medicine are the contingent aspects of its practice patterns as evident as with therapeutics, the ever-evolving outcome of the interaction between pathophysiology and pragmatics, nosology and technology. Emerging at the intersection of everything a physician can mobilize in the encounter with a patient, therapeutics—as an object of study—further affords a reflective view

back at the various factors influencing the activity of the individual physician as well as at the competing forces driving innovation and conservatism among the profession as a whole. Yet, just as in the historiography of science the history of experimental practice had until recently been overshadowed by theory-centered filiations of ideas,[6] so in the historiography of medicine had the history of therapeutics been relegated to the periphery in accounts of medicine's conceptual evolution.

Charles Rosenberg provided a key stimulus to reversing this marginalization with his challenge to historians, over two decades ago, to characterize the therapeutic changes enacted throughout the course of nineteenth-century American medicine.[7] John Harley Warner provided the most expansive response to this challenge with his epic study, *The Therapeutic Perspective*.[8] And what emerged from Warner's study was an implication of a therapeutic imperative characterizing much of American medicine since the 1800s that was counter to depictions of a bygone era's therapeutic nihilism.[9] Numerous texts have further described the dramatic transformation of American medicine between the 1880s and the 1930s, as orthodox medicine attempted to ground itself in the emerging findings of the laboratory, especially as applied in the hospital.[10] Yet little has been written, since Warner concluded his text with the advent of microbiology in the 1880s, of the history of antimicrobials from the turn of the century until the emergence of the sulfa drugs and antibiotics in the late 1930s and early 1940s.[11] In part, this lacuna stems from the foregone conclusion that—beyond preventive vaccines, quinine and salvarsan, and antidiphtherial and antitetanus serotherapy—there *isn't* much history of specific antimicrobial treatment to speak of during this era of public and private sanitation.[12]

However, such an approach not only misses an era of therapeutic transition of critical importance in the history of American medicine, but it also foregoes the opportunity to discern the origins—and appreciate the limitations—of the American medical profession's current use of the therapeutic specific. Through examining the evolving treatment of pneumonia, a dramatic view of this era emerges. It is surprising that such minimal historical analysis has been devoted to pneumonia.[13] A prevalent and lethal endemic disease lacking much of the multicolored metaphorical overlay worn by tuberculosis, its predecessor "Captain of the Men of Death,"[14] pneumonia has most often appeared—both to patients and to practitioners—in the existential guise of Death itself, apparently revealing less about its victims than about the evolving capacity and means of the medical profession to combat its ultimate foe.[15] Throughout the twentieth century in particular, approaches to the treatment of pneumonia would often serve as a barome-

ter of—and at times as a motive force behind—the changing "therapeutic perspective" held by the American medical profession.[16]

This book is divided into three somewhat chronologically overlapping sections. Part I depicts the advent of antipneumococcal serotherapy from the 1890s through the early 1930s as the epitome of the "scientifically" grounded, clinically "proven" specific. In 1892 William Osler had famously written of pneumonia: "It is a self-limited disease, and has its course uninfluenced in any way by medicine."[17] The treatment of pneumonia was grounded in physiology and the active support of the entire organism (through attention to the bowels, the circulation, etc.) while the *vis medicatrix naturae* performed its healing task. One year earlier, however, against the backdrop of the rise of immunology as a science, the first attempt at the treatment of pneumonia with antiserum had taken place in Germany.

As Chapter 1 relates, by 1913, epitomizing their efforts to introduce a bench-to-bedside research ethos in America, Rufus Cole and his disciples at the newly formed Hospital of the Rockefeller Institute in New York had demonstrated the efficacy of necessarily serologically type-specific antiserum in the treatment of (initially only the predominant such "type" of) pneumococcal pneumonia. In largely kinematic fashion, the chapter broadly traces the fortunes of antipneumococcal serotherapy in America over the ensuing two decades, from its early missionary-like spread from the benches and bedsides of the Rockefeller, through the vicissitudes of World War I, to its "proof" via clinical trials in the large hospitals of the Northeast under the care of such emerging clinical investigators as Russell Cecil and Jesse Bullowa in New York, and Maxwell Finland in Boston (each of whom, along with Cole, appear prominently throughout the book).

Chapters 2 and 3 represent an attempt to analyze more critically the novel scientific and commercial forces fostering—and fostered by—antipneumococcal serotherapy's emergence. Chapter 2 examines antipneumococcal serotherapy as emblematic of the challenge to Osler's physiology-based rationalism, which could be replaced by a focus on a therapeutic "specific" (as the immunological and therapeutic connotations of the term nicely complemented one another in this instance) aimed at the pneumococcal germ itself. As such, antipneumococcal serotherapy—driven by the rise of an applied immunology itself conventionally considered absent throughout the era—could further serve as a general example of the means by which fundamental biological research could lead to increasingly finer and more fixed disease entities and their corresponding treatments. Yet to characterize antipneumococcal serotherapy as arising solely on the basis of a self-evident applied immunology—as was done by its proponents at the time—misses, at the very least, the influence of commercial pharmaceutical forces (often

to the chagrin of such academic advocates of serotherapy as Cole himself) on the presentation of the novel specific to the profession at large. I examine this influence through "detailing" the efforts of the H. K. Mulford Company in particular.

Furthermore, as chapter 3 relates, by the early 1920s, after aborted attempts to test antipneumococcal serotherapy among flu-ridden American army base camps during World War I, calls came to base such therapeutics as much on empirically "proven" clinical efficacy as on a priori principles. The evaluation of antipneumococcal antiserum would thus serve as a focal influence in the evolution and propagation of a controlled trial ethos—as well as the embodiment of a changing approach to therapeutic evaluation broadly—throughout the interwar era in America. During the 1920s in particular, antipneumococcal serotherapy would serve as the focus of perhaps the first cooperative controlled trial performed in this country (supported by the Metropolitan Life Insurance Company, which had lost over $24 million in benefits in the wake of the 1918–19 influenza pandemic). By the end of the decade, it would be promulgated on the basis of further trials—entailing notions of alternation, control, exclusion criteria, and statistical significance—that served as a critical (and historically neglected) foundation for more extensive antipneumococcal serotherapy and chemotherapy trials in the 1930s (to be discussed in chapters 6 and 7) and the more historically commemorated trials of antibiotics emerging in the 1940s. However, by the late 1920s many clinicians continued to defend the traditional domain of individual judgment against such emerging universal standards of statistical proof. And as chapter 3 concludes, not only did type-specific antipneumococcal serotherapy largely remain limited to hospital usage throughout the decade, but the approach it entailed exposed further dramatic tensions within the profession among the perceived relative roles of specific therapy and physiology-based rationalism, the laboratory and the bedside, hospital and home, and science and art.

In response, a cadre of physicians and public health advocates would attempt to relieve these tensions while again changing the very conception of pneumonia in the process by transforming it into a public health issue, grounded in the need for centralized funding, technical assistance, and physician re-education to ensure the wider dissemination of serotherapy. This process—occurring throughout the 1930s against the backdrop of further technological innovations concerning the application of antipneumococcal serotherapy as well as the Depression, New Deal politics and polemics concerning the equitable distribution of health care, and the rise of an increasingly powerful organized medical profession in this country—is the focus of Part II.

As depicted in chapter 4, as the 1930s began, the state of Massachusetts em-

barked on an ambitious public health experiment: to bring serotherapy to the general practitioners who would see pneumonia cases in the first few days when the treatment was deemed most effective. Establishing central pneumococcal typing centers and serum depot centers across the state, along with state-provided assistance in the home-based use of the serum, the directors of the program declared it a success by 1935. By that year, New York state had equally enthusiastically initiated a "pneumonia control program," as such services came to be called. Nevertheless, as Massachusetts' experience had hinted at, and New York's experience laid bare, such a transformation of pneumonia into a public health issue engendered deep misgivings among practitioners regarding the division between private practice and public health, reflecting and at times epitomizing, the general efforts of an ever more powerful organized medical profession to resist encroachment on its authority. The result was a decidedly tenuous grounding of pneumonia as a public health concern.

In the short run, though, such a reformulation would have national consequences. As described in chapter 5, by the late 1930s the increasingly—yet to its supporters, still insufficiently—utilized antipneumococcal specific appeared as an emerging standard of care, mandating that both states and practitioners accept responsibility for ensuring serotherapy's more widespread usage. By 1940, supported by Surgeon General Thomas Parran's post-Depression attempts to redefine the domain of the public health system in the United States, nearly two-thirds of the states had developed federally funded pneumonia control programs. These programs were founded on the financial and logistical necessity of the provision of free typing and serum, yet were united with a public health approach to pneumonia entailing physician and public re-education regarding the disease, its cure, and its prevention. Such a transformation would nonetheless be fleeting, for with the advent of the cheaper sulfa drugs in the late 1930s and early 1940s, the "public health" status of pneumonia itself would soon be re-examined and discarded.

The transition from serotherapy to chemotherapeutics and antibiotics in the late 1930s and early 1940s—the focus of Part III—yields more, however, than just an insight into the consequent decline of the pneumonia control programs and a public health ethos as applied to respiratory tract infections. Rather, it offers a view of a therapeutic "revolution" that allows us to dissect the very substance of this notion and to examine the consequences of its rhetorical implementation.

As chapter 6 relates in detail, just as a cautious "calculus" had mediated the surgical "revolution" following the introduction of anesthesia nearly a century

earlier, so did it mediate the transition from serotherapy to chemotherapeutics in the context of pneumonia.[18] Antipneumococcal serotherapy had itself been deemed revolutionary in the very years and months immediately preceding (and often accompanying) the arrival of the sulfa drugs. Founded on the tenets of applied immunology, justified by controlled clinical trials, and grounded in a novel public health ethos, it had supplanted traditional physiology-based supportive therapeutics as the ideal mode of attack on pneumonia. As such, chemotherapeutics and antibiotics, with their own attendant dangers and side effects, were perceived as attractive alternative specifics rather than as revolutionary approaches to the conquest of pneumonia. Even when the cheaper sulfa drugs ultimately appeared as efficacious as serotherapy, a several-year transition ensued during which serotherapy was placed first alongside chemotherapeutics as a component of a presumably ideal "combination" therapy and later as a critical backup to the sulfa drugs. Only with the widespread advent of penicillin by the end of World War II would antipneumococcal serotherapy ultimately disappear. The antibiotic "revolution," as applied to pneumonia, thus entailed a heterogeneous transition, dependent on the coincident emergence of new drug laws and concerns, the vested interests and influence of particular clinicians, and the unique development of the pneumonia control programs themselves.

Yet as depicted in chapter 7, beyond such contingencies certain more universal aspects characterizing "modern" therapeutic change—from the interpretation and impact of controlled clinical studies to the marketing roles of pharmaceutical companies—likewise become apparent in their emerging states, both lending nuance to the depiction of the antipneumococcal therapeutic transition from 1937 to 1945 and offering a unique vantage point from which to view their own development in the post–World War II era. In particular, I explore the debate among such leading pneumonia experts as Maxwell Finland, Norman Plummer, and Jesse Bullowa regarding the interpretation of controlled clinical trials designed to test the merits of chemotherapy versus combination serochemotherapy, as they publicly set forth the very dilemmas faced (and still faced today) by practitioners in judging the internal and external validity—or freedom from bias, and degree of generalizability, respectively—of such studies. Not only would such debate take place several years before (and set the stage for) the emergence of the blinded, randomized, controlled trial of the late 1940s and beyond, but the problematizing of the data engendered would epitomize the persisting difficulties in therapeutic evaluation attendant to the ascendancy of controlled clinical trials while at the same time provide a novel space for pharmaceutical companies

to step in and provide their own cleaner (if biased) interpretations of such data to the profession at large.

Finally, pharmaceutical companies were not the only ones rewriting history. As related in chapter 8, by the end of the 1940s, the pneumonia control programs had collapsed, and antipneumococcal serotherapy had been relegated to the dark ages of medicine, if it was remembered at all.[19] The apparently revolutionary character of the transition from antipneumococcal serotherapy to chemotherapy and antibiotics had rendered obsolete all that had come before—whether serotherapy per se (appropriately so) or the public health approach it had engendered (less appropriately)—and left us on the one hand with a disease managed by individual practitioners for individual patients with (increasingly ineffective) antibiotics, and on the other with a smugness regarding our present conceptualizations and practice patterns that we would do well to explore more critically.

Methodologically, while I certainly admire historiographical efforts to place the use and evaluation of "magic bullets" within much larger social and cultural realms,[20] I have, in exploring the origins and limitations of the American medical profession's use of its antimicrobial "magic bullets,"[21] nevertheless largely focused on the scientists and practitioners themselves, though situating their evolving debate concerning the use of the specific among the changing social dynamics of their professions and fully aware that such actors are likewise continually engaged with larger social influences. In this sense, I have attempted to explore the dynamics of the medical "republic of science," to use Harry Marks's term and following many of his conceptual leads, from the inside out.[22] A large part of my research has consequently depended on published literature from both the scientific "center" (i.e., those studying the pneumococcus and its treatment) *and* the medical "periphery" (as delineated in the myriad discussions and conferences concerning pneumonia as related in state medical journals) throughout the era.[23] My reliance on these published accounts, moreover, has been augmented by an examination of the archival records left by many of the key personnel—from infectious disease specialists to insurance company executives, public health defenders to pharmaceutical distributors—who drove the therapeutic evolution related here. Many of the papers of these figures seem to me to have been remarkably underutilized to date. I hope to have at the very least provided a stimulus and guidepost (perhaps justifying the extensive footnotes) to further exploration of such figures and the therapeutic evolution they helped to drive.

SEROTHERAPY AND THE RISE OF THE SPECIFIC, 1891–1930

"Pneumonia," wrote two clinicians on the eve of antipneumococcal serotherapy in 1890, "is a representative disease."[1] From the standpoints of nosology (the classification of disease) and diagnosis, the tempo and mode of change regarding pneumonia as a disease entity over the past two millennia certainly does serve in many respects as a type for the evolution of disease concepts more broadly. From the time of the Hippocratic corpus through the nineteenth century, while the acute chills and painful cough experienced by "peripneumonia" patients were well characterized, the disease's broad dichotomization into pleurisy (affecting the lining around the lungs) and pneumonia (affecting the lungs themselves) by Anton Maria Valsalva and Giovanni Battista Morgagni in the eighteenth century constituted virtually the only attempts to place such nosology on a firmer anatomic basis. With the rise of European hospital medicine in the nineteenth century, however, René-T.-H. Laennec in Paris and Carl von Rokitansky in Vienna would correlate the antemortem symptoms and signs of pneumonia with its postmortem pathology. And the predictive capacities of the physical signs of pneumonia—based first on manual percussion (introduced by Leopold Auenbrügger in 1761) and then on auscultation through use of the stethoscope (introduced by Laennec in 1819)—could soon serve as paradigmatic examples of the power of the tools used to reveal them.[2]

With respect to changing notions of pathophysiology and consequent therapeutics, however, pneumonia would serve even more faithfully as a representative type, epitomizing the evolving "therapeutic perspective" throughout the nineteenth century in particular. As the two London clinicians cited above continued:

> Discussions as to the nature and results of inflammation have chosen it for their chief illustration, and the effect of antiphlogistic treatment has been condemned or approved upon its evidence. When depletion was most in vogue it was to the lung in inflammation that its methods were most relentlessly applied. When the wisdom of bloodletting began to be questioned, it was resolved to test its efficacy by appealing to the results obtained in pneumonia; and, coming to later times, when disease was first recognized as consisting in an orderly succession of phenomena, it was again with pneumonia that the crucial experiment was made of leaving inflammation to its own course.[3]

In America, pneumonia likewise served as a test case for clinicians to implement their changing therapeutic rationales throughout the century, from the vogue of heroic bloodletting in the early decades of the century, through the anti-heroic reaction and the increasing attention paid to the physiological support of the presumably depleted patient by the end of the 1860s.[4]

With the advent of the Golden Age of Microbiology ushered in by Louis Pasteur and Robert Koch and their colleagues in the 1870s and 1880s, such opportunities would continue to present themselves. The gram-positive diplococcal pneumococcus would—after much negotiation—be established as the primary etiological agent of pneumonia by the end of the 1880s, during the same time that immunology as a field came into being.[5] In 1884 Elie Metchnikoff had revealed the role of the amoeboid cellular phagocyte (from the Greek *phagos,* "to eat") in mediating immunity, initially demonstrated by the response of the phagocytic cells of the water flea to a fungal infection.[6] By 1888, George Nuttall, in Carl Flügge's lab in Göttingen, had revealed the in vitro activity of humoral (cell-free) factors as well, initially through demonstrating their destruction of anthrax bacilli.[7] And if the late 1870s and early 1880s had marked the onset of the discovery of infectious agents of disease, the late 1880s and early 1890s witnessed the onset of the medical attack on such pathogens through applied humoral immunology. By 1890, Emil von Behring and Shibusaburo Kitasato, in Robert Koch's lab in Berlin, had confirmed in vivo the activity of the humoral agents (soon to be termed "antitoxins," a class of what would come to be known as "antibodies"), demonstrating that their passive transfer into laboratory animals was protective against diphtheria and tetanus toxins.[8] Such passive serotherapy, or the administration of serum obtained from animals already rendered immune to a given toxin or microorgan-

ism, could thus be contrasted with active vaccination, in which the intention would be to stimulate the recipient's own endogenous production of immunity. Within a year, brothers Georg and Felix Klemperer in Berlin extended such a passive serotherapeutic approach to the treatment of pneumonia, reporting the successful treatment of six pneumonia patients with serum derived through the inoculation of rabbits with the pneumococcus.[9] Believing they had neutralized a pneumotoxin analogous to the diphtheria antitoxin, the Klemperers set in motion an antipneumococcal modality that would evolve over the course of a half-century.

The reference to diphtheria, however, is significant; and before proceeding further, it is useful to place the figure of antipneumococcal serotherapy against the more heralded ground of the attack on diphtheria. The successful treatment of diphtheria and tetanus through neutralization of their toxins with antitoxin has been recounted not only as the crowning, but often as the *only* glory of applied immunology (and especially of passive serotherapy) throughout the era between the Golden Age of Microbiology and the Antibiotic Revolution.[10] Thus, while antipneumococcal serotherapy's evolution in many ways offers unique insights into the rise and implementation of antimicrobial specifics in this century, its complementing of the history of antidiphtheria treatment serves further to demonstrate that diphtheria and tetanus antitoxins were not isolated thrusts against infectious disease throughout this era, but were rather the most "successful" representatives of a broad and persistent antimicrobial armamentarium throughout the first four decades of this century.[11]

The attack on pneumonia, in particular, thus serves as a type for both the broader successes and the ultimate limitations of antimicrobial therapy throughout this era. And the post hoc minimization of antipneumococcal serotherapy thereby represents less the ignoring of an arcane innovation than the loss of an entire perspective on the place of specifics in our modern arsenal and of the means and meaning of their implementation. Part I—through an exploration of the contentious rise of a relatively forgotten specific amidst the advent of applied immunology and the controlled clinical trial—lays the groundwork for an attempt to reclaim such perspective.

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The Advent of Type-Specific Antipneumococcal Serotherapy

The first twenty-two years of antipneumococcal serotherapy's evolution were hardly auspicious. By 1897, while the treatment of diphtheria through the neutralization of its toxin with antitoxin was being hailed as the crowning glory of laboratory science, the existence of a pneumococcal toxin itself was called into question.[1] Internationally, various researchers advocated their own antipneumococcal antibody sources—cows, ponies, donkeys, and convalescing humans to name a few—with varying degrees of success. Opinion in the United States was mixed, overall, as scientists at the turn of the century judged whether or not this was to be yet "another marvelous gift of science to the closing decade of the nineteenth century."[2] One practitioner felt so strongly about the "curative effect" of serotherapy that he stated he would consider himself culpable if he did not treat a case of pneumonia with serum.[3] Another, viewing the potential elimination of the old man's "friend" through the lens of contemporary Social Darwinism, even wondered aloud whether in some respects such a longed-for therapeutic was indeed a "boon to humanity," given that it entailed "the prolongation of life under conditions which, when nature has marked the limit, would be purely artificial."[4] To others, though, the best that could be said of serum was that it was harmless. In a review of the literature comprising 535 cases collected from dozens of small series by 1904, the prominent Philadelphia clinician James Anders revealed the standards of contemporary clinical proof in concluding: "A sufficiently extensive trial of antipneumococcal sera has been made to determine with a reasonable degree of accuracy their efficiency, and the results, as a whole, fail to carry conviction."[5] For the remainder of the decade, little would occur to change this conviction.[6]

However, in 1913 a new era in antipneumococcal serotherapy would commence in America, grounded in a redefinition of the pneumococci themselves and in the emergence of an equally novel institution constructed for the facilita-

tion of bench-to-bedside research. In Germany, Fred Neufeld had found that a given antiserum generated through the immunization of a horse with a particular strain of pneumococcus was protective upon being administered to mice against certain pneumococcal strains but failed to save the mice from others. This suggested the subdivision of the pneumococci into serological subgroups in which only members of the same subgroup, by definition, could be recognized and countered by the same antiserum. At the same time, this hinted at the possibility of a more rational clinical use of serum.[7]

In the United States, the Hospital of the Rockefeller Institute had been opened in 1910 with the explicit goal of its serving as a model for the clinical application of scientific medicine. Its first director, Rufus Cole, would remark of the hospital's mission: "In building the hospital it has not been the purpose to merely add a number of beds to the hospital facilities of greater New York. The idea has been rather to equip a hospital for a small number of patients, in such a way that the most modern methods in treatment and diagnosis could be carried out."[8] Applying the "intensive method" to the study and treatment of selected diseases, Cole hoped in particular to bring the benefits of the laboratory to the bedside of the patient.

Nearly forty years old, Cole had been a disciple of William Welch at Johns Hopkins before being chosen for the Rockefeller post. One year previously, he had visited Neufeld's lab and had been fascinated by the potential for progress against such an impassive foe as the pneumococcus.[9] In choosing "those diseases . . . in which the need for improved knowledge and better therapeutics seem most urgent, or in which the chances for new discoveries and improving the methods of treatment seem greatest,"[10] pneumonia seemed an ideal candidate.

Cole attracted such scientists as Alphonse Dochez and Oswald Avery to the problem, and by 1913 Dochez could report that the seemingly homogeneous pneumococci could in fact be divided into four groups (or "types," as they would come to be called).[11] Strains included among types I and II, comprising nearly two-thirds of all pneumococcal isolates found and studied at the time, could be differentiated by serological means (via agglutination reactions, characterized by the clumping of the organisms by antiserum) and by the capacity of type-specific antiserum to protect mice against infection with such strains. Type III strains (against which no effective immune serum could be generated) were characterized by morphologically distinct mucous capsules around the pneumococci, and a heterogeneous type IV was made up of strains against which immune serum could be generated that was active against no other strains.

For Cole, the implications were clear: "So far as immune reactions are con-

cerned the cases of pneumococcus pneumonia are caused by organisms of at least four different types, and, from the point of view of specific therapy, this is equivalent to saying that they are due to at least four organisms."[12] Antipneumococcal serotherapy had thus apparently foundered previously on account of its failure to account for the fine discriminative capacity—the specificity—of the antibodies that comprised such serum.[13] Type-specific organisms called for type-specific therapy, and failing to adhere to such rules would subject the patient to unnecessary risks and the procedure to untimely professional dismissal.[14]

By June of 1913, Cole could report at the annual meeting of the American Medical Association on the treatment of fourteen type I cases (previously associated with an approximately 25% mortality rate), all but one of whom had recovered.[15] When a pneumonia patient was admitted to the hospital, cultures would be obtained from the blood and the sputum (if no sputum could be coughed up, a direct lung puncture would be performed). The sputum would next be injected into the peritoneal cavity (surrounding the abdomen) of a mouse and incubated. After four to five hours, the exudate contained therein would be extracted and centrifuged, and the organisms obtained would undergo what would come to be known as diagnostic "typing" via agglutination reactions with type-specific antiserum. If appropriate, equine therapeutic type I or II antiserum would then be administered to the patient (Cole would soon delimit serum's usage to type I cases on account of the less-satisfactory results obtained with type II serum).[16]

The achievement of the Rockefeller group, in Cole's opinion, was less the discovery of the technique (which he credited to Neufeld) than the organization of a hospital within which such laboratory-dependent and labor-intensive diagnosis and treatment could take place.[17] And indeed, the early spread of type-specific antiserum usage would transpire in missionary fashion as Cole's group would send out serum and instructions (along with expectations for publication of results) to those colleagues willing to adopt the Rockefeller model of hospital-intensive specific treatment.[18] Such "apostles," as Francis Blake (then at the University of Minnesota) termed himself, would then spread the Rockefeller gospel to their surrounding academic and clinical communities.[19]

By 1917, though, type-specific antipneumococcal serotherapy would garner national attention through two related events: the mobilization of United States troops for World War I, and the publication by the Rockefeller group of a how-to monograph on serum administration. As early as 1915, the U.S. Army had requested of the Rockefeller group information regarding the serum treatment of pneumonia;[20] and at the mobilization camp in El Paso, Texas, an unexpected epidemic of lobar pneumonia arose in the winter of 1916–1917, with a mortality rate

of over 20 percent. Through interaction with Simon Flexner and Cole at the Rockefeller Institute and Augustus Wadsworth at the New York State Board of Health, the camp's medical staff acquired ten liters of type I antiserum and enough white mice to initiate a campaign against type I pneumococcal pneumonia. By August of 1917, Major Henry Nichols could report an 8 percent mortality rate among 63 serum-treated type I cases, compared with a 39 percent mortality rate among eighteen type I patients not receiving serum.[21] As Nichols tersely summarized: "In economic terms, out of 400 cases, 100 men can be saved at less than the cost of burying them."[22]

The Rockefeller group would be quick to include Nichols' report in their monograph as a paradigmatic example of the emerging dangers of the pneumococcus amidst winter camp conditions as well as of the potential weapon placed at the military's command.[23] Moreover, while serum was still considered as most appropriately used in the hospital, it was now to be promoted (much, as will be seen, to Cole's later consternation) as conceivably given anywhere, as long as boiled water, iodine, and alcohol were available.[24] The army was intrigued. By the onset of American involvement in World War I, the surgeon general's office had made the serum treatment of type I pneumonia "obligatory,"[25] committed to purchasing 25,000 copies of the Rockefeller monograph to distribute to the entire medical corps,[26] and sent a large number of army medical reserve officers to the Rockefeller to master pneumococcal typing and serum administration.[27] Cole would serve with Welch on a wartime Pneumonia Board, visiting several of the camps;[28] and his disciples from the Rockefeller would themselves fan out to camps across the country.

Nevertheless, the wartime experience with type I antiserum engendered mixed responses. For Nichols, the therapy was "revolutionary," leading him to declare that the "method of treatment has passed the experimental stage and no case of type I infection who dies without the early intravenous administration of large doses of type I serum can be said to have received the best treatment."[29] For a significant number of investigators, though, its benefit was suggestive but not definitive;[30] and for still others, serum was a disappointment, given the advance buildup.[31]

Indeed, a number of circumstances worked against achieving a favorable wartime consensus. Chief among these, of course, was the explosive influenza pandemic of the late fall and early winter of 1918, which led to a sense of panicked urgency in the wake of an endless procession of respiratory disease.[32] Not only were a proliferation of antipneumococcal remedies utilized—from the refined Rockefeller serum to both normal and convalescent human serum,[33] polyvalent

chicken serum (i.e., serum from fowl immunized against multiple "types" of pneumococci),[34] and autolyzed pneumococcal antigen (entailing the supposed "active immunization" of patients)[35]—but as would be appreciated soon thereafter, they were administered with few parallel control cases.[36]

In addition, when serum was used, it was often administered in "shotgun" fashion, with little concern for the responsible organism itself.[37] Even before the onset of the influenza pandemic, information from the army had been difficult to interpret in the setting of poor diagnostic typing technique and often-insufficient serum administration.[38] With the onset of the pandemic, even such relaxed standards were dismissed. As Henry Chickering lamented to Cole: "Of course our plans for careful study had to be abandoned and it became a problem to find a bed for the patient and keep him in it and give him a drink occasionally. . . . It became impossible to type each case so I made a great effort to obtain post mortem lung cultures on every case but here again the embalmers beat me out."[39] Under military conditions, moreover, the usual types I and II pneumococcal pneumonia were no longer found to predominate in many camps; in the setting of such preexisting respiratory diseases as measles and influenza, secondary *Streptococcus hemolyticus* pneumonias began to emerge,[40] while among the pneumococcal isolates, a vast majority were found to be type IV and hence not amenable to Cole's serum.[41] Finally, among those with type I infections who could potentially benefit, two men died as a result of anaphylactic reactions to serum.[42] Whereas prior to the war nonfatal anaphylactic reactions had been reported out of Johns Hopkins,[43] through the war experience, not only had serum's range of benefit come into question, but it had become stigmatized by the potential for fatal side effects as well.[44]

To the Rockefeller coterie, well aware of camp conditions, the published military reports on serum utilization appeared worthless. Grumbled "apostle" Francis Blake to Cole: "The perusal of many of the reports that appear from week to week in the Journal of the A.M.A. tend to fill me with wrath except for a saving sense of humor. Of course it is not to be wondered at after one has become familiar with the quality of the bacteriological work that is carried on in most Base Hospital Laboratories. . . . It is rather a shame, however, that so much trash gets into print."[45] To nonbelievers, though, the unchecked ascent of antipneumococcal serotherapy merited reevaluation at this time.[46] Two devastating reviews, in particular, would appear in the early 1920s. William Thomas, at St. Luke's Hospital in New York, and Edwin Locke, at Boston City Hospital, challenged Cole's results on three interrelated points: first, that Cole's cited mortality figures for historically untreated type I pneumonia were inflated (i.e., whereas he had cited a

figure of 25–30%, they would cite a mortality rate of 11% among soldiers, and 18–20% among Boston City Hospital patients); second, that the serum itself, in both their own institutions and as evidenced by a review of the cumulative wartime experience, did not yield the dramatic reduction in mortality achieved at the Rockefeller; and third—and most critically—that such critiques themselves were necessary in the first place because no adequate trial of serotherapy had been attempted in the setting of parallel untreated *control* cases.[47] Simply put, the authority of Cole, while impressive, was to be subordinated to the emerging authority of statistical evidence (as will be discussed at length in chapter 3).[48]

For Cole (whom Thomas had directly consulted and apparently ignored prior to publishing his article), such critiques could be dismissed out of hand: not only did the cited untreated type I mortality figures strain credulity, but the conditions under which serum had supposedly been tested were entirely inadequate.[49] As he considered: "I have always maintained that treatment with serum is a very laborious and time-consuming matter and has to be done with much care. To base an opinion as to the effectiveness of the method upon most of the present reports is like rendering a decision in regard to the results of appendicitis operations, basing the conclusions upon operations performed by general practitioners on kitchen tables!"[50] Indeed, convinced he had established the efficacy of type I serotherapy under ideal conditions, Cole by this time was concerned less with the additional diffusion of his technique than with the further biological elucidation of the pneumococcus in an attempt to uncover new approaches to the treatment of the other serotypes (against which he regarded serum as relatively ineffective).[51]

Others, however, were more hopeful. Locke's study did not dismiss antipneumococcal serotherapy altogether. It had long been noted that such serotherapy worked best when "administered early and in large doses."[52] Locke found that at least among Boston's most prominent hospitals, pneumonia mortality was indeed halved when serum was administered within the first three days of disease onset.[53] The keys, then, were to produce a more potent serum, and to make it easier to administer as soon as a patient was admitted to the hospital.[54]

Contemporary researchers seemed ready to achieve such goals. At the H. K. Mulford Company, F. M. Huntoon had in 1920 produced a concentrated "polyvalent" (again, containing serum apparently effective against more than one serological "type" of pneumococcus at once) antibody solution by using adherent bacteria themselves to separate the antibodies from unwanted serum proteins. And at Harvard, Lloyd Felton would in 1924 develop a concentrated antiserum (soon produced in both monovalent and polyvalent forms) through the precipitation of

serum globulins in distilled water.[55] In direct contrast to the Rockefeller ethos of necessary specificity, some practitioners could thus choose to administer polyvalent serum empirically in the setting of lobar pneumonia. They could then either await typing results before narrowing their serum to monovalent therapy, or simply use the typing results for prognostic information (i.e., type I cases would benefit far more from serum than would type II cases, which would in turn benefit far more than would type III cases).[56]

Moreover, and likewise in striking contrast to Cole's reliance on case series and historical controls for "proof" of serum efficacy, a second generation of pneumonia experts emerged who were prepared to test the results of such novel sera against those obtained with parallel "control" patients not receiving antiserum. Their shared ethos of "control," emerging in the aftermath of the study (in 1898) of diphtheria antitoxin by using alternate patients as controls who would not receive the novel therapeutic modality (as will be discussed in chapter 3), would receive critical institutional backing through the intervention of the Metropolitan Life Insurance Company. After Met Life had paid out over $24 million in benefits to cover 68,000 excess deaths among its policyholders in the wake of the 1918–19 influenza pandemic, Lee Frankel, the head of the company's Welfare Division, organized an influenza commission for the study and reduction of respiratory disease.[57] It would be headed by Milton J. Rosenau, a leading public health figure and former director of the U.S. Public Health Service's Hygienic Laboratory (which would, in 1930, become the National Institutes of Health). Frankel considered that among influenza cases, secondary pneumonias (rather than influenza itself) were "practically always" responsible for killing patients.[58] And with his network of agents having already interacted with public health departments across the country during the influenza epidemic, Frankel had both the means and the will to tackle influenza and pneumonia as problems national in scope. As such, the commission sought to unite in purpose—and to direct the efforts of—every important pneumonia research group in the country (with the exception of the Rockefeller group).[59] Indeed, Rosenau could report to Frankel by 1921 that not only was the extent of the commission's reach "unique," but that it had filled the very gaps engendered by the lack of coordinated federal or state approaches in this respect.[60] Public health departments across the country were implored to cooperate,[61] as Frankel and Rosenau attempted to create a commission poised to attack influenza and pneumonia wherever they might recur and to coordinate (and co-opt) researchers wherever they might reside.[62]

By 1921, just as Cole was losing interest in serum's widespread dissemination, the Influenza Commission turned its own attention to serum's potential utility,

with an ultimate intention to fund controlled studies among clinicians at multiple collaborating institutions. Of these, Russell Cecil, working at New York's Bellevue Hospital, would offer the first results in 1922. Having patients on six wards at the hospital treated with Huntoon's solution, and those on six control wards "treated in practically the same way" except for the receipt of antibodies, he could report a reduction in type I mortality from 22.2 percent to 13.3 percent, and in overall mortality from 28.3 percent to 21.4 percent. Unfortunately, while apparently efficacious, the Huntoon's solution also seemed responsible for severe thermal reactions upon administration, resulting in three iatrogenic fatalities (and, in one surviving patient, a temperature rise to 113°) among the 424 treated patients.[63]

Thus, the collaborating institutions turned to Felton's concentrated antiserum (itself developed under Influenza Commission auspices); and by the late 1920s, they had produced a trio of mutually reinforcing "controlled" studies championing concentrated serum's utility in type I cases. At Bellevue, Cecil had turned from designating alternate wards to alternate individual patients as controls. All lobar pneumonia patients with even hospital numbers "promptly" received treatment with concentrated polyvalent antiserum (the average time to serum administration was 18 hours from admission, and the antiserum was considered de facto bivalent for types I and II only), while odd-numbered patients served as controls, "in other respects . . . treated in the same way as the patients who received serum."[64] Once again, Cecil found a reduction in mortality among 300 type I patients, from 32.6 percent among the controls to 20.9 percent among the serum-treated.[65]

At Harlem Hospital, Jesse Bullowa collaborated with William H. Park, the city's Department of Health director who had first positioned New York City at the worldwide forefront of diphtheria antitoxin production thirty years earlier. Bullowa likewise alternated patients, but he treated patients with Felton's polyvalent antiserum only until typing results returned, at which time appropriate monovalent therapy was substituted. His results, better still than Cecil's, were a 45 percent reduction in type I mortality among over two hundred patients, from 31 percent to 17 percent, with nearly a 50 percent reduction in mortality among fifty-six type I bacteremic patients (i.e., those patients found to have pneumococci growing from their blood cultures, associated with a dramatically higher mortality rate), from 71 to 36 percent.[66] Both hospital studies, moreover, demonstrated a modest concomitant reduction in mortality among type II patients that, while far less impressive than the type I results, at least justified the use of polyvalent serum.

When Maxwell Finland, at Boston City Hospital, confirmed such type I results with bivalent Felton antiserum in 1930 (ironically, essentially continuing the same studies Edwin Locke had initiated there a decade earlier), serotherapy at last appeared to its vocal supporters to possess clinical substantiation to match its justification on a priori immunological principles.[67] A contemporary newspaper account declared:

> It required the combined efforts of five universities and scores of laboratory workers to produce the ammunition which is to lay low the pneumonia germ, and . . . it has been demonstrated by the most exacting experiments in the hospitals of this city [New York] and elsewhere. It has been put to every test, has been studied by the medical fraternity and is declared to be a great forward step. . . . As the use of the bacteria serum spreads, such inroads will be made upon pneumonia that within a few years the disease will be as under control as diphtheria.[68]

The trio of studies appearing by 1930, in particular, would serve as the scientific apotheosis of this novel immunologic specific, both redefining the necessary criteria for therapeutic justification and exposing the schisms among the clinical community that was to administer this supposed boon to its patients. The following two chapters will discuss in greater detail such shifting criteria of justification—as well as the powerful resistance offered against these changes.

A "Specific" Specific and the Turbid Age of Applied Immunology

In the first edition of his *Principles and Practice of Medicine* (1892), William Osler placed pneumonia, not within the section on specific infectious diseases, but under "diseases of the respiratory system."[1] Lamenting that "we have, then, no specific for pneumonia," Osler perhaps nowhere else so firmly expressed a belief in the *vis medicatrix naturae,* arguing for supporting the functioning of the body's organs while nature took its course.[2] Disagreeing with the scripture of Osler, Rufus Cole and his own "apostles" instead elevated the role of the therapeutic specific on the basis of immunological specificity itself, considering that universally applicable antipneumococcal antiserum functioned because of the type-specific interaction between antibody and pneumococcus. At the same time, they redefined in tandem the notion of nosological specificity, stating that pneumococcal pneumonia could, paradigmatically, be subdivided as a disease entity on the basis of the serological subdivision of the offending pneumococci themselves. And while commercial pharmaceutical houses would be quick to seize upon and popularize Cole's elevation of the therapeutic specific, their uncoupling of such elevation from the tenets of humoral immunological specificity—as well as from Cole's correlated notion of nosological specificity—would reveal approaches and motivations differing markedly from Cole's.

A "Specific" Specific

To understand the radical nature of Cole's introduction of a specific for pneumonia, it is helpful to review briefly the history of this concept in American therapeutics. John Harley Warner has certainly shed the most light on the issue, maintaining that antebellum American therapeutics entailed the need to individualize disease treatment in the context of all of a patient's contingent attributes

(from age and sex to race, temperament, and geographical location), while specifics represented the very types of quack empirics that ignored such individualization.[3] By the 1860s, however, these antebellum principles had begun to wane as a generalizing rationalism, founded on the emerging universal principles of physiology, began to overshadow the individualization of treatment.[4] As such, the therapeutic empiricism acquired through clinical experience was to be ascribed to the *art* of medicine, while the emerging physiology-based rationalism was to be considered medicine's *scientific* basis.[5] Under such precepts, according to Warner, precise physiological monitoring could partially replace wanton drugging in the "control" of the patient,[6] and such an approach would dovetail nicely with an increasing belief in the *vis medicatrix naturae* as exemplified by Osler.

Warner, however, further credits "physiological therapeutics" with re-legitimizing the notion of "specific" treatment, since particular drugs could be expected to generate universally specific physiological effects.[7] With the advent of bacteriology in the 1870s and 1880s, moreover, a novel connotation could be given to the specific in the context of a novel reformulation of disease itself. If the ontological notion of disease-as-germ could replace that of disease-as-physiological dysfunction, then a specific could be envisioned as an agent capable of the universal destruction of such fixed responsible entities. Warner notes that throughout the 1880s bacteriology failed to support the rise of a new class of such specifics. But by the 1890s, with the emerging findings of humoral immunology fueling the imagination of clinicians on both sides of the Atlantic, Osler's approach was considered by some clinicians to be outdated by the time it had been published. For such clinicians, the application of physiology-based rationalism was to be consigned to the art of medicine, while the application of novel specifics was to be based on the experimental findings of science.

Scattered expressions of this emerging ethos can be found with respect to pneumonia as early as 1892, the same year that Osler's *Principles* went into print. Upon treating a patient with convalescent serum, two Philadelphia clinicians would declare a profound role for contemporary insight into immunity: "The day is dawning when we shall cure disease, instead of, as heretofore, guided only by empirical and often fallacious experience, endeavoring feebly to aid the *vis medicatrix naturae,* like the blind groping in the dark."[8] Of course, such expressions of hope were by no means universal. Twelve years later, for example, William Welch (who in 1892 had treated the Klemperers' findings with the utmost caution) would continue to deny the existence of a "specific" for pneumonia.[9]

Nevertheless, within a decade, Rufus Cole would directly refute his mentor's claim through the almost literary conflation of the immunological and therapeu-

tic connotations of the term "specific." In his presentation on serotherapy before the American Medical Association in June of 1913, Cole would first invoke the immunologic term "specific" to discriminate between his own usage of type-specific antiserum and the historically indiscriminate usage of commercial sera against even non-pneumococcal pneumonias, stating that such "serums are as rigidly specific in their immune reactions as is antidiphtheric serum for diphtheria toxin."[10] By the end of the same presentation, though, in his declaration that "a method has been devised for the successful specific treatment of at least a portion of the cases of acute lobar pneumonia," Cole had given the term "specific" a more traditionally therapeutic connotation.[11] Serotherapy had gone from being immunologically specific to being a universal specific.[12]

Running in parallel to such a transformation, moreover, was a fundamental redefinition of the pneumonias—and pneumonia patients—themselves. Prior to Cole's approach, the nosological spectrum of pneumonias against which antiserum was reported to be effective could be arrayed in various ways. Although the most prevalent was constructed along anatomical grounds (with lobar pneumonia to be differentiated from bronchopneumonia, for example), one Cincinnati physician felt free to report, with an eye to underlying patient characteristics: "The range of applicability of the serum would seem to be coequal with the distribution of the disease. Thus it has been successfully employed in aggravated senile pneumonia, in pneumonia of pregnant women and in pneumonia complicating various forms of cachexia and acute rheumatism."[13] In direct contrast, for Cole the nosology of pneumonia was to be based solely on the microbiological agents responsible for the disease in the first place. And regarding pneumococcal pneumonia in particular, a circular set of referents entailed that immunological specificity both defined pneumococcal specificity and determined the consequent therapeutic specificity of antisera. Far from being just a linguistic trope, immunological specificity appeared to be precisely what rendered Cole's therapeutic specific superior to previous attempts at serotherapy. Cole would spend the next two decades elaborating on the consequences of such mutually reinforcing definitions of specificity for the clinical approach to pneumonia.

Such a reformulation rendered anatomical distinctions among pneumonia cases less important, if not meaningless. Time spent obsessing over whether a given case signified lobar pneumonia or bronchopneumonia was time lost before the obtaining of an accurate microbiological specimen and the subsequent commencement of specific treatment.[14] Underlying patient characteristics and predispositions were to be comparatively minimized in such nosological and therapeutic schemata, coincident with the relative marginalization of physiology-based

rationalism as applied to the pneumonia patient.[15] Conversely, serologically revealed distinctions among the pneumococcal specimens obtained translated into distinct disease entities themselves.[16]

Cole's system would soon have adherents. As Francis Blake would spread the gospel before an audience in Minneapolis in 1917: "The indiscriminate use of antipneumococcus serum, without a preliminary determination of the immunological type of the infecting organism in every case, is a procedure which would be just as illogical as an attempt to cure tetanus with diphtheria antitoxin, in as much as the immune serum can be effective only against the homologous type of pneumococcus."[17] Laurence Litchfield, a colleague in Pittsburgh, would that same year report of his own converted Western Pennsylvania brethren: "We believe it is just as necessary to differentiate one type from another as it is to differentiate pneumonia from typhoid fever."[18]

By 1927, Cole would take such an analogy to its logical extreme. In his De Lamar Lecture given at the Johns Hopkins School of Hygiene and Public Health, Cole drew a lengthy (and thereafter frequently cited) analogy between the separation of formerly vague intestinal ailments into such microbiologically defined entities as typhoid fever and bacterial dysentery, and his own separation of the pneumococcal pneumonias caused by various pneumococcal serotypes. For Cole, moreover, such a process of nosological redefinition was relevant not only for pneumococcal pneumonia but could also serve as a general example of the means by which biological research could lead to increasingly finer and fixed specific disease entities and correspondingly specific preventive modalities and treatments.[19] With an implicit thrust at attention given to vague constitutionalism, he exposed this underlying rationale: "A number of the most serious ills, from which man suffers, attack not only the decrepit and infirm but also the most strong and robust. To prevent the occurrence of these diseases, the weapon must be suited to the game. General measures no longer suffice. The epidemiologist, as well as the physician, must also use specific measures, and . . . these measures are likely to be effective only in so far as they are based on knowledge of the essential nature of the disease which he is combating."[20]

Antiserum and Applied Immunochemistry

Cole's statement, of course, implies that after the rise of applied immunology in the 1890s on the shoulders of the serum treatment of such toxin-mediated diseases as diphtheria and tetanus, clinicians and scientists continued to look to immunology for a class of antimicrobial "weapons." This is by no means an ac-

cepted wisdom. As was earlier noted, Arthur Silverstein has cited the failures of immunologists by the turn of the century to combat tuberculosis, cholera, and syphilis to conclude that both active immunization and passive serotherapy fell into decline after 1910. Immunology, in this characterization, transformed into immunochemistry, a basic science without a clinical driving force or application (as it apparently would remain until the rebirth of cellular immunology in the post–World War II era).[21]

Nevertheless, this characterization may be directly challenged by acknowledging the therapeutic imperative that continued to compel clinicians, scientists, and pharmaceutical houses in the aftermath of the parallel rise of microbiology and immunology. The fictional Max Gottlieb of Sinclair Lewis's 1924 classic, *Arrowsmith,* synthesizing potentially curative antibodies in vitro, was indeed a product of his times.[22] Prior to the advent of the sulfa drugs and antibiotics in the late 1930s and 1940s, clinicians and scientists employed a host of antimicrobial approaches. Ranging from chemotherapy itself (most famously, Paul Ehrlich's Salvarsan for syphilis) to the use of ingested "friendly" bacteria to eliminate more pathogenic strains (e.g., *Lactobacillus acidophilus* in the treatment of bacillary dysentery), to Felix d'Herelle's use of the bacteriophage against diseases ranging from cholera to plague (immortalized in Lewis's novel), the approaches were all more or less grounded in their advocates' models of immunity and host defense.[23] Regarding passive serotherapy in particular, Simon Flexner had, in the decade prior to Cole's introduction of type-specific antipneumococcal serotherapy, himself introduced antimeningococcus serotherapy for the treatment of meningitis. And in the first decades of this century, serotherapy had been introduced with varying degrees of consequent popularity for the treatment of entities ranging from such toxin-mediated bacterial diseases as scarlet fever to such virally mediated diseases as poliomyelitis.[24] Indeed, in January of 1921 the *Journal of the American Medical Association* ran a twenty-one-article series on the merits and limitations of "biologic therapy."[25] No such therapy, however, was as firmly intertwined with emerging American immunological findings and theorizing as antipneumococcal serotherapy.

Critically, the potential therapeutic application of antipneumococcal serotherapy not only rested on such findings, but in many instances it *drove* such research in the first place.[26] Alphonse Dochez, in presenting the immunological classification of the pneumococci before the American Medical Association in 1913, reflected that "the problem in the beginning was approached with a view of obtaining, if possible, a specific therapy."[27] Cole's correspondence—as well as much of the contemporary justification of the Rockefeller Hospital—seems to

bear this out.[28] Olga Amsterdamska has further substantiated this statement with her analysis of the career of Oswald Avery, who came to work with Cole in 1913 and would focus for over three decades on the pneumococcus. While Avery's research would of course result in such fundamental discoveries as the chemical analysis (with Michael Heidelberger) of specific pneumococcal polysaccharide haptens (molecules capable of being recognized by antibodies) in 1923, and the still more heralded identification (with Colin MacLeod and Maclyn McCarty) of DNA as the transforming principle in the switch of pneumococci from rough to smooth phenotypes in 1944, Amsterdamska argues, his entire career of investigating the pneumococcus was driven fundamentally by a search for the clinical cure of pneumonia.[29] Years later Colin MacLeod would reflect on Avery as the "applied scientist": "It can be said without hesitation that the fundamental studies Dr. Avery and his colleagues carried out on the pneumococcus had as their goal the understanding of the disease. The disease was the rallying point; this kept everybody's eye on the ball."[30]

In this process, however, specific antipneumococcal serotherapy was to be distinguished by its advocates from empiric antipneumococcal therapies through its grounding in the experimental immunology and microbiology taking place at such centers as the Rockefeller, Johns Hopkins, and Harvard.[31] As early as 1902, a serotherapy-supporting clinician from Maryland had harked back to previous Hopkins research on the elusive pneumotoxin, declaring: "A foundation had been laid upon which, in time, we should be able to build a rational scientific treatment of this disease. . . . We have outgrown empiricism and tradition."[32] Two decades later, after the putative pneumotoxin had been replaced by the type-specific polysaccharide capsule surrounding the pneumococcus as the target of antiserum attack, the underlying ethos of scientific rationalism nevertheless persisted unabated:

> It seems a safe statement that in no disease have such a multitude of specific remedies been advocated as in pneumonia. . . . But a few have had even a reasonable theoretic basis, and none have been the result of sound experimental study. All have been empirical. . . . A brief review of a few of the more fundamental researches in immunity directly bearing on the serum treatment of pneumonia will serve, I hope, to show on what a thoroughly scientific foundation such methods rest.[33]

Fundamental immunology and serotherapy were to be envisioned as mutually reinforcing, as the bench-to-bedside ethos of the Rockefeller was both to reflect and to further enhance the continued rise of scientific rationalism.[34]

Indeed, the "specific" rationale underlying antipneumococcal serotherapy, as

mentioned previously, would directly parallel the overall immunological consensus emerging in the first decades of the twentieth century. After the concomitant emergence of cellular and humoral immunology in the 1880s, proponents of the two modes of defense had, in the ensuing years, bitterly debated the relative importance of the cellular phagocyte and humoral antibodies in host defense. While some degree of compromise had been achieved through Sir Almroth Wright's invocation of opsonization (i.e., that antibodies could somehow prepare bacteria for ingestion by cellular phagocytes), attention would soon focus far more on the specific recognitive capacity of the antibodies than on the blindly gluttonous phagocytes and other components of "nonspecific" immunity (i.e., protective substances and cells lacking the precise discriminative capacity of antibodies).[35]

This led to a dismissal by Cole and his followers of the potential "nonspecific" benefits of immunotherapy in general; and Cole, who would serve as president of the American Association of Immunologists in 1921, was not without influence. Even when a study apparently demonstrated the successful nonspecific use of autolyzed pneumococci in the active vaccine treatment of pneumonia—incorporating alternate cases as controls, and with an overall reduction in mortality from 38 to 23 percent—its author, expressing the field's ignorance regarding such nonspecific benefits, was practically apologetic in requesting that the treatment be considered as a backup to type I serum administration.[36]

The snobbery of specificity became still more apparent when its advocates had to contend with the occasional findings that patients with type IV pneumonias appeared to benefit from serotherapy, that patients enrolled in further trials of obviously nonspecific immunotherapies likewise occasionally appeared to benefit more than their untreated counterparts, and that occasional patient subsets in both situations appeared to improve precisely in the setting of marked "chill" reactions (or "thermal" reactions, often characterized by rigors) regarded as mediated by nonspecific protein reactions. As one public health official meekly wrote to Cole of what he had witnessed from the chill reactions: "In the field work my cases are not as well controlled as yours and I think your figures would be more accurate. I am perfectly aware of the good results of the serum and I am perfectly sure that it is due to its specificity but I am inclined to think that those having chills make a little more decided [and] clear cut improvement than those who do not have a chill."[37] Responding to such claims, advocates of specificity could retort that perhaps undetected specific antibodies were themselves at work in the first setting and that no experimental basis had been established to justify the benefits of nonspecific therapy in the latter two settings.[38] In other words, nonspecific immunotherapy, hiding without experimental evidence behind the lus-

ter of immunology, was to be regarded by Cole and his colleagues as nothing more than an empiric.

Instead, the Rockefeller researchers and their colleagues would focus on the role of specific humoral immunity in mediating the dramatic natural "crisis," the critical turning point when a seemingly dying pneumonia patient would suddenly reverse course and defervesce, with a parallel resolution of clinical toxicity.[39] Indeed, this quintessential clinical event—"such a clear-cut, striking phenomenon that it would seem that it may depend on some single cause or relatively simple biological reaction, such as the destruction of the bacteria by immune substances or neutralization of toxin by antitoxin"—was to be redefined in immunological terms.[40] Dochez, in 1912, demonstrated that type-specific "protective antibodies" generally first appeared in the blood of stricken patients at the time of the crisis.[41] Moreover, Fred Neufeld himself had nearly a decade earlier laid the foundation to bridge such findings with cellular immunology by demonstrating that antipneumococcal antiserum could function as an opsonin (terming it a "bacteriotropin" in this capacity) and somehow render pneumococci amenable to phagocytosis.[42] By 1913, Paul Clough at Johns Hopkins demonstrated that the peri-crisis protective bodies functioned as opsonins for consequent type-specific phagocytosis;[43] and within two years, Carroll Bull at the Rockefeller would demonstrate that (at least among rabbits) such preparation for phagocytosis appeared to transpire through type-specific agglutination.[44] Thus, antipneumococcal resistance would serve as a paradigmatic example of specific immunity at large, and serotherapy would serve as an artificial augmentation of the natural—but at times insufficient—humoral process.[45]

Furthermore, the basis of such frequent natural insufficiency would soon receive its own reinterpretation—this time in the context of the very immunochemistry conventionally considered to have been devoid of clinical application. In 1917 Dochez and Avery reported their identification, both in cultures of living pneumococci and in the blood and urine of pneumonia patients, of a free substance capable of being precipitated by type-specific antiserum. Historically, the elucidation of the nature of this "soluble specific substance" by Avery and Michael Heidelberger (in 1923) as a polysaccharide capable of an antigenicity (i.e., a capacity to stimulate an antibody response) formerly ascribed to proteins alone has been regarded as revolutionizing the very tenets of immunochemistry.[46] Nevertheless, from the time of its discovery, the substance was interpreted in terms of its potential clinical utility. Doubtful that the mysterious substance served as a toxin analogous to those of diphtheria and tetanus, Dochez and Avery had still initially noted that its excessive presence in the urine was correlated with a high

mortality rate; the substance in the urine could thus serve qualitatively as a diagnostic aid in typing, and quantitatively as a prognostic aid.[47]

For Cole, moreover, the soluble antigens appeared as representative munitions from the very contest between the antigen-leaking bacteria and the antibody-loosing host, with the substances serving to neutralize the host antibodies, and the clinician hoping to counter this process and influence the fortunes of immunochemical warfare in the host's favor.[48] Francis Blake, in a year filled with conducting medical investigations at army bases, would flesh out the military metaphor still further in his attempt to elucidate which "factors serve to tip the balance favorably or otherwise in the struggle between antigen and antibody."[49] In noting the correlation between the development of precipitans (types of antibodies), the disappearance of antigens from the patient's urine and bloodstream, and clinical improvement, Blake would summarize: "In those patients who fail to excrete soluble antigen during the course of the disease, it is probable that the development of precipitin in the body keeps pace with the elaboration of the antigen and that the two serve to counterbalance or neutralize each other until finally at or about the time of crisis the development of precipitin exceeds the formation of soluble antigen, and free precipitin appears for the first time in the blood."[50] The epic battle between the Captain of the Men of Death and the patient had thus been reduced to a struggle between antigen and antibody; even the very differences in mortality exacted by the varying types of pneumococci could be reconstructed as secondary to the relative proficiency with which the germs could synthesize soluble specific substance.[51]

By the late 1920s, as it became apparent that the protective capsules surrounding the pneumococci were themselves composed of the same specificity-defining polysaccharide substance, such a model continued to serve as the immunochemical rationale for the serum treatment of pneumonia.[52] In diligent hands, moreover, such an approach could be taken to its logical extreme through the actual titration of antiserum against the changing concentration of antigen in a patient's bloodstream. Advanced in 1928 by Harlem Hospital's Jesse Bullowa, such intensive treatment represented a literal translation of bench-to-bedside medicine, the apotheosis of the fluid relationship formed between basic and applied immunology.[53]

Enter Commerce

Clinicians and researchers, from the 1910s through the 1930s, were proud to base therapeutics on such a glorious new science as immunology.[54] And antipneumococcal antiserum advocates, in particular, were proud to contrast their ap-

plication of basic science with the use of blind specifics.[55] When victory over pneumonia could be demonstrated, it was consequently to be portrayed as a triumph of both bedside and bench, as demonstrated by the public commendation of Russell Cecil by Benjamin White, director of the Massachusetts Department of Health's Biological Laboratories: "His perseverance has been due to the fact that he has looked at pneumonia not only from the standpoint of a clinician but also from the standpoint of a bacteriologist and immunologist."[56] However, such clinicians protested too much in their separation of applied immunology from therapeutic empiricism and the marketplace which encouraged it. And in concluding this section, it is instructive to situate their self-assessments, both to lend nuance to the image of American antimicrobial therapeutics in the first decades of the twentieth century and to demonstrate further the longstanding nature of the linkages and tensions between the medical academy and commerce.

Immunotherapy was as far from a commercially free field as those reflecting on *Arrowsmith* (and its fictional Dawson T. Hunziker company) would expect.[57] As a real-life representative, inspired by the rise of applied immunology in the 1890s, the H. K. Mulford Company of Philadelphia had become the nation's foremost commercial producer of biologicals, starting with its diphtheria antitoxin in 1895 (and extending to, among other biologicals, the introduction of antipneumococcal antiserum in 1899).[58] By 1910, writes Jonathan Liebenau, Mulford boasted 950 employees and $3 million in annual sales, and could use its marketing apparatus to shape clinicians' and patients' expectations regarding the benefits of serotherapy as a whole.[59] By 1912, the company would begin publication of *The Mulford Digest,* claiming: "There have been many demonstrations (the history of the microscope, e.g., and the telescope, point this out) that the scientific and altruistic spirit of the 'men of business' or of 'commerce' is often perfectly pure and of great service to humanity. Most desirable is the spirit of cooperation between all who work for the extinction of disease."[60] Nevertheless, despite their accurate (if vocal) differentiation of their operation from those of their competitors on the basis of their own strict adherence to standardization of units and purity of product,[61] Mulford's brand of antipneumococcal immunotherapy was in direct contrast to Cole's despite their own efforts to cloud such distinctions.

For example, the American Association of Immunologists had actually derived in 1913 from the Society of Vaccine Therapists, a group of scientists wishing to uphold the tenets of vaccine therapy (i.e., vaccination given in the setting of actual disease in order to stimulate further the natural immune response), which had been initiated by Sir Almroth Wright a decade earlier.[62] However, as specific passive serotherapy was increasingly favored over active vaccination in the treat-

ment of pneumonia throughout the 1910s and 1920s, Mulford would continue to promote its antipneumococcal sero-bacterins (used for active vaccination) alongside its passive serotherapy products.[63] By 1913, one page after describing Cole's elucidation of pneumococcal specificity, they would reprint from the *North American Journal of Homeopathy* a case report of the use of Mulford Pneumo-Bacterin in the active treatment of pneumonia.[64] Three years after the widely disseminated Rockefeller monograph on the treatment of acute lobar pneumonia had entirely ignored active vaccine therapy, Mulford's marketing forces would continue to be positioned to augment general sero-bacterin sales, exemplifying the rise of the "detail man" itself through the following suggestions:

> To insist that each Mulford representative detail an average of at least three physicians each day, on biological products. To insist that every man's sales include a fair proportion of biological business, particularly serobacterins. . . . That we prepare a set of about ten cards carrying short, snappy sentences about serobacterins and mail same to all salesmen, all contract customers, and try a concentrated campaign in a limited area, by mailing the same cards to all physicians in certain territories, and finishing the campaign with a four-page insert giving more complete information regarding serobacterins.[65]

Even concerning passive antipneumococcal serotherapy, Cole had impressive adversaries in the polyvalent serotherapy-supporting "men of business."[66] In its publications, Mulford attempted to blur the distinctions between its efforts and those of the Rockefeller, implying (when it suited them) a continuum between its own pre- and post-Cole efforts:

> Antipneumococcic serum is not infrequently referred to as "the new treatment" for pneumonia, whereas Tyson states in his practice of medicine [1906] that pneumonia was one of the first diseases suitable for serum treatment and gives due credit to the Mulford Laboratories for having first produced Antipneumococcus Serum commercially. Since its production by the Mulford Laboratories in 1899, Antipneumococcic Serum has been improved from time to time in accordance with the discoveries of research workers conducting their investigations in the Rockefeller Institute and the Mulford Laboratories at Glendolen.[67]

Yet supporting an unconcentrated polyvalent serum more amenable to "the demands of the general practitioner, situated remote from medical centers and without facilities for biological diagnosis, as well as those who are more fortunately situated in relation to great medical centers and hospitals,"[68] they contrasted their own humanitarianism with the ivory-laboratory leanings of Cole:

> According to Cole, pneumonia is a disease in which treatment should never be undertaken outside a hospital. In the larger cities it may be possible for many patients to take advantage of hospital treatment and laboratory diagnosis. For a large proportion of pneumonia patients, however, the plan is not feasible. Must these cases then be deprived altogether of the possible benefit resulting from [polyvalent] serum therapy . . . ? With these factors in view, and in the belief that the general practitioner should have the opportunity of deciding, . . . the Mulford Company is continuing their preparation of antipneumococcus serum.[69]

Cole—who devoted a good deal of energy to personally monitoring the commercial antipneumococcal antisera in particular, hoping, in an era of only informal regulation, to be able to work collegially with the commercial houses in the guise of quality control—didn't buy the story, considering it "written for the express purpose of selling their polyvalent serum."[70] Rather, he intended to apply the advice of his colleague, Lawrence Litchfield, who upon returning from a visit to the Mulford home offices asked Cole "to bring as much influence as possible to bear on the Mulford people against their argument that humanitarian obligations demand the promiscuous use of a shotgun serum by the rank and file of the medical profession in all cases of pneumonia."[71] The self-serving arguments of the commercial houses were to be refuted, and the inadequacies of their sera in particular were to be exposed when appropriate.[72]

On the one hand, Cole, if anything, underestimated the men of commerce in the monovalent/polyvalent exchange. In January of 1918, Mulford's president had approved a measure to "push the sale of such serums as are not made and distributed generally by State Boards of Health, etc., always emphasizing the superiority of Mulford Products."[73] Within a year, this meant pushing the sales of polyvalent antipneumococcal serum "by inserts and otherwise;"[74] and by the following winter, their efforts had apparently been successful, as "reports from the sales department indicate that nearly all physicians favor Polyvalent antipneumococcic serum, and that there is very little demand for Antipneumococcic Serum, Type I, II, III."[75]

On the other hand, Cole would claim a degree of success in his interaction with industry. By 1918, he had become largely satisfied with the commercial serum products.[76] Two years later, it would be at the Mulford Laboratory that Huntoon would develop his widely respected (if not unequivocally by Cole, and if not for long) concentrated antibody solution, reflecting the general rise in the quality of research (and the increasing affiliation with academic institutions) among pharmaceutical companies throughout the interwar era.[77] And still further, the mar-

keting efforts of Mulford and such competitors as Parke Davis would further the rise—even if uncritically—of applied immunology (and, by extension, antipneumococcal serotherapy) throughout the era.[78]

Nevertheless, the notion of an applied immunology unsullied by empiric claims, as championed by antipneumococcal serotherapy's advocates, certainly represents its own obfuscation of contemporary history. Furthermore, in denying the relative importance in establishing serotherapy of apparent therapeutic efficacy as opposed to the "basic science" on which such therapeutics was purportedly founded, those championing the role of bench research likewise obscured a second developing branch of science that not only could be used to contest commercial claims based on a priori principles,[79] but at which certain of serotherapy's advocates would likewise stand at the vanguard: clinical epidemiology, as predicated on the validity of the controlled clinical trial. Chapter 3 thus concludes Part I with an examination of the manner by which the intense evaluation of antipneumococcal serotherapy would help drive the development of the controlled clinical trial in this country and consequently shape the very manner of therapeutic evaluation generally, while at the same time exposing divisions among practitioners expected to make sense of the resultant claims of serotherapy's supporters.

Fundamental Tensions

Clinical "Proof" and Clinical Resistance

The treatment of pneumonia—on account of the disease's marked variability in severity from patient to patient and from year to year—had long provided a challenging yet alluring subject for those concerned with the methodology of "proving" therapeutic efficacy. Pierre Louis, for example, had in the 1830s used "pneumonitis" as the principal object of his "numerical method" (comparing the mortality rates of patients divided into unequal treatment groups) in challenging the efficacy of bloodletting.[1] By the era of serotherapy, the disease retained its enigmatic variability. Such variability, by the turn of the twentieth century, was felt to "render general statistics wholly unreliable in determining the efficacy of any plan of treatment" if such statistics were based on either small case reports or the use of historical controls.[2] Yet by the end of World War I the concentration of pneumonia patients in hospitals in America provided clinical researchers with a unique opportunity. It soon became apparent to a core group of researchers that the experimental immunological science underlying serotherapy should be accompanied by an equally reproducible clinical science capable of separating the inherent clinical variability of pneumonia from the effects of therapy. Controlled clinical pneumonia studies would hence serve at the vanguard of a gradually changing approach to therapeutic evaluation; and the treatment of pneumonia would likewise serve as a litmus test regarding clinicians' evolving "therapeutic perspectives" themselves.

Antipneumococcal Serotherapy and the Propagation of the Controlled Clinical Trial

The degree to which studies of antipneumococcal serotherapy—as well as the general interwar development of the alternate controlled trial—have been ig-

nored in most recountings of the evolving clinical trial is surprising. The conventional account begins with biblical references to comparative studies, proceeds through James Lind's eighteenth-century evaluation of scurvy remedies, and advances through such nineteenth-century applications of the numerical method as Louis's researches and Ignaz Semmelweis's studies of the prevention of puerperal fever.[3] Critically, it next fixes on Johannes Fibiger's use of *alternate controls* (treating patients admitted on alternate days differently, to be precise) in establishing the efficacy of diphtheria antitoxin in 1898, as well as the contemporary efforts of Karl Pearson in Britain to establish biometry as a medical science capable of rendering reproducible statistical distinctions between treatment groups.[4] From Fibiger and the early biometricians, the story next moves to the advocacy of "randomization" by Ronald Fisher for agricultural experiments in the 1920s (i.e., through using random strips of land to allocate treatment versus control groups, local environmental influences would be eliminated); to the popularization of such techniques for clinical medicine through Fisher and A. Bradford Hill in the 1940s (i.e., through the selection of treatment versus control groups on a random basis, the bias incurred through selecting patients to treat would be eliminated); and, ultimately, to Hill's subsequent combination of randomization with "blinded" evaluation of clinical outcome (i.e., ignorance on the part of the assessors to which therapeutic group a particular patient had been assigned) in the British Medical Research Council study of streptomycin for tuberculosis in 1948.

In moving from Fibiger to Hill, linkages are generally depicted as stuttering and fragmentary,[5] or even nonexistent.[6] The rise during the intervening era of the *structural* elements that would make possible the advent of large-scale randomized controlled trials has been the subject of more sophisticated recent analyses. These include Harry Dowling's and Harry Marks's depictions of the Cooperative Clinical Group study of syphilis in the late 1920s and early 1930s as the origin of multicenter collaborative efforts in America, Nick Rasmussen's investigation of the evolving American clinician-industry arrangements in the conduct of trials, Desiree Cox-Maksimov's relating of the rise of state "machinery" and legitimization for the running of large-scale trials in Britain, and J. Rosser Matthews' focusing of attention on the rise of statisticians (such as Raymond Pearl in the United States and Major Greenwood in Great Britain) and their attempts at establishing a professional stronghold in medical research.[7] Such accounts, however, still miss critical elements contributed and embodied by the intense evaluation of antipneumococcal serotherapy in America. When serotherapy is mentioned at all in the above accounts, it is done so dismissively at best,[8] in-

accurately at worst.[9] This is unfortunate. The clinical debate among antipneumococcal serotherapy's advocates in America (both with each other and with the therapy's detractors) reveals the gradually increasing and diffusing appreciation of the elements of control and bias in clinical trials in the era between Fibiger and Hill.

To fully appreciate such an emerging ethos, it is important to understand the background from which it emerged. With respect to the evaluation of antidiphtheria antitoxin, the early success of the Fibiger trial, along with the general belief in the antitoxin's efficacy, precluded more extensive alternate controlled diphtheria trials in America in ensuing decades.[10] But the novel antipneumococcal antiserum provided the ideal substrate not only for conducting such trials but for debating their very legitimacy. Indeed, the use of the controlled clinical trial was not merely met by ignorance: it often faced active opposition along logistical, epistemological, and ethical lines in the first three decades after its introduction.

Paradigmatically, Cole—leading the charge to bring the results of the laboratory to the bedside—nevertheless did not expect that the *methodology* of the bench could be translated to the bedside, and he would in fact serve as a leading opponent of the emerging ethos of clinical "control."[11] At one level, such opposition derived simply from the daunting logistics of the clinics' acquiring enough patients to divide into sufficiently large treatment and control groups when more basic methods of proving therapeutic utility (from laboratory to animal studies to case series and the use of historical controls) were already available. Using the diphtheria lesson as a warning rather than as an inspiration, he remarked before the American Medical Association in 1917: "To establish by statistical evidence the value of any therapeutic agent in lowering mortality requires much time and the accumulation of a very large number of cases. . . . The evidence of other kinds, however, has been so striking and the mortality statistics, so far obtained, so good that we cannot but feel hopeful that the treatment of this type of infection by immune serum is of distinct value."[12] His concerns would be shared by several prominent colleagues.[13]

Such logistical concerns, moreover, were accompanied by a deeper dubiousness about the clinician's capacity to apply the experimental concept of "control" to as heterogeneous an assemblage of studied objects as patients (as opposed to more standardized laboratory animals) in the first place.[14] By 1922 the New York pneumonia investigators were assuredly aware, furthermore, of the findings from the control wards of Russell Cecil's Bellevue Hospital study (discussed in chapter 1), where Alexander Lambert had reported variations in mortality ranging from 14 to 64 percent among wards.[15] For Leo Kessel and Harold Hyman (up-

town at Mount Sinai), demonstrating an antebellum conception of the role of patient characteristics in mediating disease progression, the rote reduction of the individual pneumonia patient to the average case of a controlled study was thus an inherently flawed process, revealing the epistemological untenability of medical statistics themselves. Making no apologies for the lack of controls in their own test of Huntoon's solution, they declared: "No simultaneous control series was run. The uncontrolled variables, such as (1) age of the patient, (2) day of admission, (3) type of invading organism and (4) degree of bacteremia, render a "control" series a remote gesture. In the last analysis the results of therapy in lobar pneumonia will rest a great deal more on clinical judgment than on statistics."[16] Cole was marginally more charitable, using the pure studies of the bench as the ideal toward which clinical studies could only aspire: "Superficial clinical evidence" required the fundamental support of "more refined observations" rendered in the laboratory with patients' serum samples to merit validity.[17]

Consequently, since Cole and his colleagues had demonstrated the efficacy of serum in the test tube, through animal experimentation on monkeys, and through case series, the division of patients into control and treatment groups would be more than time-consuming—it would be ethically suspect. Refuting the doubting Thomas and empirical Locke, Cole would righteously reply: "It has been asserted that in such a study of a therapeutic agent evidence may be obtained only by carrying out simultaneous controls and therefore that only alternate cases should be treated. . . . However, as soon as our studies gave evidence which convinced us, at least, that this form of treatment was useful, we did not feel justified as physicians in withholding a remedy that in our opinion definitely increased the patient's chances of recovery."[18] Echoing the sentiments of *Arrowsmith*'s Gustaf Sondelius in challenging Martin Arrowsmith's controlled study of bacteriophage therapy among a plague-ridden island population, Cole implied that the unimpeachable information already acquired at the experimental level rendered the treatment of the individual patient more justifiable than withholding the individual's treatment in pursuit of as flawed an enterprise as a so-called controlled study.

However, echoing the supporters of the numerical method in nineteenth-century France, an emerging cadre of clinicians envisioned that evolving modes of clinical evaluation would offer the most valid appraisal of a given therapy's merit. Alfred Gray, in reporting his study of pneumonia treatment with Preston Kyes's polyvalent chicken serum in 1920, remarked of the serum: "The above announcement [by Kyes, in 1911, of the successful production of antiserum] was made after laboratory experiments, both *in vitro* and *in vivo,* had demonstrated high antibody content in the serum and its protective action in laboratory ani-

mals. . . . The next step was to determine its therapeutic value in man. Extensive therapeutic testing is the final proof of the value of any curative serum."[19] For Gray, reporting from one of the first controlled studies of antipneumococcal antiserum (conducted at Camp Grant, in Illinois), such an ethos of control emerged from the exigencies of serum supply and demand in the wake of the influenza epidemic: "There was no preparation for control comparison. . . . But when it became apparent that there would shortly be more cases of pneumonia than serum could be furnished for, it was decided to restrict its use to cases in a single ward for ease of administration until more serum should become available."[20] However, for Kyes himself (conducting his own trial of the polyvalent serum at Cook County Hospital), not only was the use of control wards a crucial a priori principle for the evaluation of serotherapy's efficacy, but the allocation of the patients studied by an admission office "without discrimination" and without "selection of favorable cases within the ward where the serum treatment was employed" was deemed critical to the validity of the results obtained.[21]

By the 1920s, such efforts at careful control would underlie the design of a lineage of antipneumococcal trials. At a conference of the Oklahoma State Medical Association in 1923, one local practitioner commented on a proposal for the treatment of pneumonia with ethylhydrocupreine (a chemotherapeutic agent): "The most scientific way of reaching conclusions regarding treatment of a disease, as variable in degree as is pneumonia, would be to take alternate cases in a large hospital service, treat the even numbers with the routine management and the odd numbers with the new drug. If the series is sufficiently large, conclusions could then be drawn which would be of value."[22] But such assertions emanated most emphatically from the very vanguard of serum therapy in Boston and New York, encapsulated in Edwin Locke's stinging critique:

> The proof of the possibility of producing an active or passive immunity against Type I pneumonia in certain animals, or even of curing the pneumonia in infected animals by the intravenous injection of homologous serum, does not establish its value in man. Nor do these results of animal experimentation warrant the acceptance of conclusions from clinical tests that are not based on the most exact clinical observations. To be fully trustworthy, it is absolutely essential that therapeutic results, whether the agent employed is a drug or an immune serum, should be checked by a control series.[23]

As mentioned in chapter 1, this ethos of "control" would be most forcefully advanced by the Metropolitan Life Insurance Company's Influenza Commission in the decade after the influenza pandemic of 1918; and at the heart of the commis-

sion seems to have resided Lee Frankel's own belief in the necessity for controlled evaluations of potential preventive and therapeutic interventions. In the rough draft of a letter prepared in 1919 for Haley Fiske (president of Met Life) to deliver to the company's home office staff, requesting their voluntary cooperation in an antipneumococcal vaccination effort, Frankel had initially written of the "distinctly encouraging" reports of such vaccination to date:

> Unfortunately, observations, however favorable, without acceptable scientific controls, do not furnish information that is authoritative. We know that diseases fluctuate considerably by seasons, years, and periods of years; that an apparent decrease in any given disease may be due to a coincidence of causes not embraced in the particular treatment under investigation. Thus, the value of antitoxin in diphtheria was proven by the steady and constant (though fluctuating) decrease in mortality where it was conscientiously employed as compared with the higher, also fluctuating, average of deaths where it was not used.[24]

The section was omitted from the official letter Fiske sent off to his staff, but the ethos of control would be fundamental to the various influenza and pneumococcal vaccination efforts the Influenza Commission would first support in locations scattered across the country.[25] Moreover, by the winter of 1920–21, as the vaccination efforts were proving worthless for influenza and less than conclusive for pneumonia, the commission lent its weight to the study of antipneumococcal antiserum, with the ethos of control intact.[26]

They first supported Cecil's evaluation of Huntoon's solution at Bellevue Hospital, with six control wards serving as a comparison for six treatment wards. For Cecil, since the apparently unbiased admitting office assigned patients to the wards with "no selection of any kind," the control was deemed "a fair one from every point of view."[27] But while such supporters as Huntoon would laud the "adequate control used in this series,"[28] perhaps the inter-ward variability in mortality led to a revised approach to control when the Influenza Commission prepared for a multicenter evaluation of serotherapy's efficacy in the winter of 1923–24. Intending to support concurrent hospital studies in New York, Philadelphia, Boston, Cincinnati, and Chicago, the commission outlined the following Plan of Procedure:

> 1. In every hospital cooperating in this study, there should be some one person responsible for, and having general supervision of, the experiment. 2. Each ward will be considered an experimental unit. Every case of lobar pneumonia admitted to a particular ward will be numbered consecutively. . . . 3. Every case receiving an even

> number shall have the antibody treatment. The odd numbered cases will not receive antibody treatment, but in other respects will be handled like the antibody cases. . . . 4. In order to minimize the personal equation in the diagnosis and effect of treatment, it is necessary that both the antibody and control cases come under the direct observation of the same person, in each experimental unit or ward.[29]

In retrospect, of course, it is apparent that the commission placed an enormous amount of faith in the capacity of the supervising physicians to ensure equivalent nonserological treatment and evaluation among the serum recipients and controls. Moreover, considerable variability existed among the hospital protocols, ranging from the type of serum used to the mode and timing of administration. Nevertheless, it would be the ethos of control that would apparently remain central to the commission's collaborative inquiry.[30]

By the late 1920s, the most outspoken proponent of this ethos was Jesse Bullowa, who was leading the trials of antipneumococcal antiserum at Harlem Hospital. As mentioned in chapter 2, Bullowa was likewise a leading advocate of the bench-to-bedside model articulated by Cole, but Bullowa held out far higher promise for clinical trials to approximate their laboratory counterparts in statistical validity. Speaking before the New York Academy of Medicine in December of 1927, Bullowa articulated the critical elements of a controlled trial: (1) the notion of strict alternation, such that "there must be no selection of patients. . . . Only the order of arrival in the ward determines whether a patient is to receive serum";[31] (2) the assurance that such alternation has been effective by using a "severity rating" to rank each case upon admission on a 100-point scale (with respect to such elements as cardiovascular, respiratory, gastrointestinal, and neurological status), thereby permitting a post hoc comparison of treatment outcomes stratified by severity classes;[32] (3) a clearly articulated set of criteria for the consistent "rejection of patients" deemed inappropriate for the study;[33] (4) and finally, a standard test to determine if, and when, the differences between the treated and control groups would be "statistically significant."[34]

For Bullowa, this question of "when" addressed the ethical questions raised by Cole regarding "how can we determine the number of cases necessary for a judgment," or more explicitly, "how long we were justified in continuing to deprive patients in the control series of what may be a valuable and available therapeutic aid."[35] Tied to the question of *if,* the question of *when* depended on contemporary biometric notions concerning the probability that observed treatment differences between two studied groups were secondary to chance alone. If the ratio between the differences in mortality between two groups and the "standard error of differ-

ence" calculated for the two groups (itself reduced the larger the number of patients enrolled) was greater than two, reported Bullowa, then the difference would have less than a 5 percent probability of occurring by chance alone and would be deemed statistically significant and hence indicative of the true effects of the therapy.[36] Bullowa could only report a suggestive but nonsignificant ratio between the serum-untreated and the serum-treated type I patients of 1.9 (34%–18% / 8.3%) in his 1927 address; but by late 1928, he had indeed enrolled enough patients to achieve a statistically significant difference.[37]

Such efforts certainly appear to have influenced the development of the controlled trial at large. The Bellevue alternate controlled study disproving the utility of digitalis in pneumonia in 1930—considered by Lilienfeld as *the* source of "refinement of design . . . using the alternate control method" in the interwar period—was in actuality itself directly foisted on the "machinery [of the antipneumococcal antiserum studies] that could readily be adjusted to include an investigation of the effects of the use or nonuse of digitalis as routine therapy in this disease as well."[38] Moreover, the collaborative trials among the New York and Boston hospitals would, it seems, directly influence—and certainly anticipate in every regard—the historically vaunted British Medical Research Council Therapeutic Trials Committee's evaluation of antipneumococcal serotherapy (in which A. Bradford Hill appears to have played a critical role) begun in 1931 and itself considered a direct conceptual link to the MRC's streptomycin trials.[39] Moreover, in propagating contemporary biometric methods, Bullowa would himself anticipate A. Bradford Hill's own classic presentation on therapeutic comparisons.[40]

The extent to which such a statistical ethos diffused in the 1920s and 1930s is difficult to assess, but it was certainly prevalent enough to inspire both satire and caricature. In Lewis's *Arrowsmith,* Martin, as a medical student, argues with the professor of materia medica, Dr. Lloyd Davidson, regarding the efficacy of memorized remedies:

> "Dr. Davidson, how do they know ichthyol is good for erysipelas? Isn't it just rotten fossil fish—isn't it like the mummy-dust and puppy-ear stuff they used to give in the olden days?"
>
> "How do they know? Why, my critical young friend, because thousands of physicians have used it for years and found their patients getting better, and that's how they know!"
>
> "But honest, Doctor, wouldn't the patients maybe have gotten better anyway? Wasn't it maybe a *post hoc, propter hoc?* Have they ever experimented on a whole slew of patients together, with controls?"

> "Probably not—and until some genius like yourself, Arrowsmith, can herd together a few hundred people with exactly identical cases of erysipelas, it probably never will be tried! Meanwhile, I trust that you other gentlemen, who perhaps lack Mr. Arrowsmith's profound scientific attainments and the power to use such handy technical terms as 'control,' will, merely on my feeble advice, continue to use ichthyol!"[41]

By 1933, after discussing before the New England Physical Therapy Society the many contemporary remedies advanced for pneumonia, Dwight O'Hara (who had actually served as the first pneumonia resident at Boston City Hospital and who would eventually serve as dean of the Tufts School of Medicine) would take the place of Davidson in mockingly concluding of such a litany: "Of course, no self-respecting investigator will neglect to arrange a 'control series.'"[42]

The ethos of the controlled clinical trial, while certainly more prevalent during this era than traditionally appreciated, thus continued to face resistance to its wider acceptance. Even among advocates for the use of statistics in medicine, the inherent validity and generalizability of controlled studies remained in question. Max Finland, noting the unfavorable age distribution and duration of disease among the control as opposed to the treated cases from the supposedly "controlled" studies conducted at Boston City Hospital in the 1920s, questioned the very capacity of contemporary study designs to eliminate "unconsciously exercised" bias among researchers.[43] Equally fundamentally, several observers wondered aloud whether the Northeast hospital-based results could be generalized to less homogeneous conditions. Reflecting a persistent (if markedly diluted from its antebellum heyday) ethos of broad regionalism, for example, one New Orleans practitioner would report of the New York and Boston studies: "I think the question we all have to realize is we have a little different problem to deal with than they have in the East, and we will have to get up our own statistics."[44]

But what concerned the proponents of antipneumococcal serotherapy more than challenges to the validity and generalizability of their studies was whether the typical general practitioner, who "often bases his use of a therapeutic measure on his own experience and that of his friends," would apply the findings from controlled studies in the first place.[45] To some degree, it appears they underestimated the practitioners. Wrote one Gleason, Wisconsin, practitioner to the "Director [of the] Rockefeller Institute for Medical Research":

> If one, engaged in private practice, would have an average fatality rate of one percent for Pneumonia of all types for thirty years and a lower rate for the last fourteen years, he would like to compare the results of his treatment with other procedures

> or to use controls. But the use of controls in private practice is not advisable. May I ask, how one can get access to a hospital, where he can have co-operation so as to be able to use controls and to ascertain by laboratory experiments the value or lack of it of the several procedures and drugs employed and proposed.[46]

To a vernacularly significant extent, though, as reflected in contemporary discussions of the utility of antipneumococcal serotherapy, the emergence of statistics in medicine continued to face resistance from many academicians and practitioners. Huntoon himself, after acknowledging before the Medical Society of New Jersey that mortality statistics for any given therapy would require an enormous number of cases to attain validity, thereby deduced the requirement, not for large trials, but rather for the substitution of an individual's accumulated clinical impressions.[47] Representative of a still more fundamental persistence of faith in individual judgment over cold statistics, a West Virginia practitioner, while admitting to having never used serum, proceeded to advocate before his county medical society the use of veratrum viride, given that his father had obtained "excellent results" with the vasodilating drug.[48] And epitomizing such disdain for statistics, a Kansas practitioner, after poignantly relating before his state medical society the deaths of his mother, brother, sister, and son to pneumonia, would follow: "I do not wish to bore you with statistics. In fact statistics in this case are of little value—contradictory, and often misleading."[49]

Such contemporary tensions are perhaps best exemplified by a debate that ensued after Huntoon's above-noted presentation of serotherapy before the New Jersey State Medical Society in 1928. John Kolmer, an erstwhile and well-known advocate of the wonders of immunotherapy, in relating his own conversion to a faith in antipneumococcal serotherapy as occurring against the backdrop of a child's remarkable recovery, had seconded Huntoon's advocacy of individual judgment over universal statistics. Thereafter, however, he was challenged by a local practitioner who essentially summarized the emerging contemporary statistical ethos in his own polite attack:

> I feel we ought to say a word, too, in regard to judging the value of a new treatment by the method of personal impression rather than statistics. I know that the method of personal impression is the one that the doctor likes to accept, but if you will remember the history of therapy of pneumonia by that method, by this time we would have had thousands of specific cures. . . . I do not wish to imply by this that the careful clinical observation and impression in the hands of very conscientious and reliable persons is not important, but I think we must agree that the final proof of a new method of treatment must be by statistical methods, particularly in pneumonia

> which varies so much in different years, in the severity of the epidemic, and the virulence of the infection, and in the specific reaction of individuals. I am afraid if we ever adopt the impressionistic method of interpreting therapeutics we will be having a setback again in the accurate estimate of therapeutics.[50]

Huntoon, however, would be given the final word on the topic, exemplifying the enduring resistance to such universalism: "You will have to admit that clinical observation extended over a sufficient number of cases and a sufficient period of time is just as valuable as statistics. You take the accumulated experience of a man who has used this specific treatment and listen to what he says."[51]

Thus, the evaluation of antipneumococcal antiserum serves as a barometer of—much as, at times, it served as a focal point for—the evolution of therapeutic evaluation in America in the first decades of the twentieth century. It epitomizes the tensions between an emerging universal biometric science and traditional notions of individual judgment. Indeed, the rise of antipneumococcal serotherapy as a novel specific, derived from immunological research and championed via the use of statistically interpreted clinical trials, did not transpire in a vacuum. At each stage in its evolution, the therapy would further encounter and engender resistance, reflecting tensions among the perceived relative roles of specific therapy and physiology-based rationalism, as well as among the roles of the supporting conceptual and technological structures necessary for their implementation, as the American medical profession continued to redefine itself in the early decades of the twentieth century.

Resistance

These tensions were not confined to pneumonia alone. Naomi Rogers, for example, has demonstrated the parallel debate emerging in the 1910s and 1920s among clinicians with respect to the diagnosis and treatment of poliomyelitis (another of the few diseases chosen by Cole to study upon the Rockefeller Hospital's inception).[52] Yet pneumonia provided a crucible for such tensions, perhaps owing not only to its widespread prevalence but also to the inherent conflicts already characterizing the approach to its treatment by the turn of the century. On the one hand, the inability of the medical profession to reduce the toll of the Captain of the Men of Death since the discovery of the pneumococcus had led to a sense of urgency and even desperation.[53] Pneumonia had not only surpassed such traditionally feared infectious diseases as typhoid and tuberculosis in its annual toll, but it was emerging, not as the old man's friend, but as the young man's fiercest

foe.[54] In the wake of the influenza pandemic of 1918–19, moreover, it would become "the despair of clinicians everywhere, regardless of their position in the medical profession or their facilities for handling the disease."[55] On the other hand, the endless litany of failed pneumonia therapies engendered a strong cynicism toward novel remedies: "In the days of Benjamin Rush and Thomas Watson, bleeding, blisters, calomel and antimony were the weapons, and for the last 75 years quinine in one area, veratrum in another, aconite in another, creosate in another and digitalis in another have had their faithful adherents. This is the age of bacteriology and sera, and it is natural that in the centers these should have their adherents."[56] Often such competing concerns appeared side by side in public discussions of pneumonia,[57] leading to a full spectrum of consequent responses—from the nihilistic lament that "nine out of ten get well, and the tenth one the devil himself can't save,"[58] to an attempt at maintaining a therapeutic "center" amidst the therapeutic proliferation engendered by the deadly disease,[59] to the strident call that "no stone should be left unturned toward clearing the way for a positive, efficient management of this disease."[60] Thus, the secondary tensions generated concerning the roles of specifics and science must be understood in the context of this already heated environment.

Such secondary tensions were still more intense, given the fundamental therapeutic principles at stake. Regarding physiology-based rationalism (the application of universal principles of physiology to the support of the human organism, as discussed in chapter 2), Osler's apparent therapeutic impotence was no longer acceptable to advocates of specific therapy: "Supporting measures, such as digitalis and oxygen, judiciously applied, and careful nursing are of great importance, but are of no avail in the presence of an overwhelming infection, or in the absence of specific resisting powers on the part of the host. Any marked reduction in the mortality rate in the disease once established can come only through the application of some form of specific therapy."[61]

This pro-specific ethos, however, would strike a harsh chord amidst the chorus of Oslerian disciples in spirit. For some, the general search for specifics themselves was to remain a noble but often elusive task.[62] For others, the misguided application of such searches' erroneous findings would at the least interfere with the *vis medicatrix naturae,* which had "developed a specific treatment" of its own and was "oftentimes a better physician than art."[63] At the worst, the quest was less elusive than dangerously illusive, as the "lunatic fringe" of medicine fell for the potentially deadly commercial mirages pitched before them—at the expense of their patients.[64] More commonly, though, specifics were feared less for their

inherent toxicity than for their drawing of attention away from the application of physiology-based rationalism.[65]

The strongest such critique emerged from Bellevue itself, where Harlow Brooks, despite his own tentative approval of type I antipneumococcal antiserum,[66] nevertheless sternly reminded clinicians that they were "treating a patient with an inflammatory condition of his lungs rather than some specific, definite, and unmixed infectious process."[67] In actively caring for the patient through paying attention to his or her physiological status and through relieving his or her symptoms, the clinician could affect the clinical outcome as much as via the mightiest of specifics.[68] As though deconstructing the gendering of treatment that had emerged between the physician's use of specifics and the nurse's attention to patients' symptoms, Brooks would conclude:

> It is very true that as yet we have little to offer in the way of real treatment of pneumonia as a specific disease, but we have a tremendous field of effort which we may cultivate for the patient's relief. Stay with your patient as much as possible. Shape every sign and symptom to his benefit—that is the sort of "nursing" that cures pneumonia. Your close study and the application of your general knowledge of disease and therapeutics applied to the crisis as it develops may win the fight. You will, I doubt not, save many cases which would have otherwise died by just this individual study which I have suggested to you. You may not "cure pneumonia," but you can many times give life where but for you and your knowledge and effort death would have taken place.[69]

What was at stake, of course, was the very foundation of the active therapy of pneumonia: the new specifics borne of the microbiology and immunology laboratories versus the modalities borne of an ethos of physiology-based rationalism. Not confined to the wards of Bellevue, such tensions were strikingly exhibited in 1925, for example, at a meeting of the Medical Association of Georgia. An Atlanta practitioner, pronouncing that "the greatest thing in pneumonia, as we all know, is to determine what the heart is going to do," followed the outline of his system of monitoring and responding to the needs of the cardiac pump with a terse dismissal of specific serum therapy, stating that for pneumonia cases it was not "worth a dam[n]."[70] In a stirring abdication of gentlemanly behavior, a fellow Atlantan would characterize such a claim as an example, not of a competing therapeutic system, but of ignorance of the emerging rational approach to specifics: "That [claim] is based upon the fact that he must not know anything about serum or about biology. I based my statement [in support of type I serum] upon careful

study of immunology and biology."[71] A new scientific approach rested on a new science, to work in tandem with, if not to supersede, traditional modalities; and resistance to such progress was to be condemned as ignorance or obstinacy.

Alongside the debate over the relative roles of novel specifics and traditional supportive care, moreover, emerged a parallel negotiation regarding the relative roles of the laboratory and bedside investigations of the individual patient. Followers of Cole's reconstruction of pneumonia nosology along microbiological rather than anatomical lines could carry his approach to its logical extreme: based on a suggestive history, they could even diagnose pneumonia "in the laboratory before the appearance of any characteristic physical signs."[72] Applied to therapeutics, as in the previously noted titration of antiserum to soluble specific substance, laboratory methods could transform the modest general practitioner into the commander of a technological arsenal. As Bullowa wrote: "The modern treatment of pneumonia requires as much organization as the treatment of a patient suffering from a surgical condition. . . . This method of treating pneumonia requires more from the physician than the expectant method. It requires more equipment than a prescription pad and stethoscope."[73] A Chicago physician—citing how his team, "misled by [a patient's] apparent clinical improvement and her temperature reactions" and failing to confirm such superficial symptoms and signs of improvement through laboratory demonstration of an adequate antibody titer, tragically lost a serum-treated patient after her initial defervescence—carried the laboratory ethos to its moral extreme.[74] And while such extremes were rarely imitated, they served as the tip of a large laboratory dried iceberg. Joel Howell has demonstrated, for example, that at the Pennsylvania and New York Hospitals during this era, the taking of complete blood counts of pneumonia patients rose from 3.7 and 8 percent to 100 and 83 percent respectively, while the use of chest x-rays increased from 0 to 47 and 42 percent respectively.[75]

Nevertheless, as Howell elsewhere notes (in the context of the approach to the diagnosis of appendicitis around the turn of the century, in particular), such a transformation engendered resistance among those who challenged the emerging authority of the laboratory and staked their medical authority on the mastery of bedside medicine.[76] This resistance would further emanate, in the case of pneumonia, from clinicians across the country who lacked either the inclination or the means to rely on typing and laboratory monitoring in the application of antipneumococcal antiserum.[77] Again, however, the most forceful articulation of resistance emerged from the same New York centers from which antiserum was being advanced. Charles Camac, medical director of Bellevue, critiqued the re-

liance upon laboratory rather than clinical criteria for the evaluation of clinical efficacy from a pragmatic standpoint:

> The research laboratory worker is compelled to limit his statements to what is demonstrable by laboratory tests. The clinician, at the bedside, *lacking these laboratory proofs,* makes observations with regard to duration of the disease, well-being of the patient, that is degree of toxic manifestations, limitation of the pathological process, recovery, mortality, etc., all of which, if studied in a sufficiently large number of cases and within strict limitations, constitute *clinical evidence* which may precede and lead to subsequent laboratory proof.[78]

Brooks, his colleague, would more forcefully apply such a critique to the level of the individual patient. Much as in arguing that the use of specifics would preclude the use of physiology-based rationalism, he warned that excessive laboratory diagnostic probing and analysis was not only impractical but potentially dangerous:

> As you know from the teachings of your pathologist and of your bacteriologist, there are several, even many kinds of acute pneumonia, but in so far as the therapeutist is concerned much of this detailed knowledge is unnecessary, even inadvisable, if it be secured at the sacrifice of the patient's rest, through a delay in treatment, or if your basis of treatment be determined by theoretic conjectures and busy-body and exhausting examination. . . . The gross clinical aspects of the case are almost always of more consequence than any of the more detailed data secured by the finer methods of study.[79]

Once again, an infatuation with the technology of the laboratory was to be tempered by a healthy respect for time-honored, individualized examination and treatment at the patient's bedside.[80]

Finally, between 1892 and 1930, the percentage of deaths in Massachusetts from respiratory disease taking place in the hospital, as opposed to the home, rose from 11.2 to 43.1 percent.[81] And enmeshed with such concerns over the relative roles of specifics and physiology-based rationalism, technology and personal judgment—and further taking place against the backdrop of the tremendous trajectory of the role of the hospital in American medicine[82]—a corollary debate emerged concerning the proper place of treatment of the pneumonia patient. For example, L. A. Nippert, one of the most strident advocates of individualized physiology-based rationalism, had stated before the Hennepin County Medical Society in Minneapolis in 1920 that a 50 percent reduction in mortality could be obtained by having patients receive "good care" from their families at home.[83] He

was immediately challenged, however, by a fellow Minneapolis practitioner, who tied his contrasting advocacy of hospital-based care to a faith in the promise of emerging specifics (such as type I antiserum).[84] In general, throughout the 1920s and early 1930s, there was little published advocacy for the home-based use of antiserum; conversely, the most strident public calls for home-based treatment came from clinicians who failed to make any mention of serotherapy whatsoever.[85]

Such a dichotomization almost hints at an incommensurability between the various approaches to the disease. Indeed, one can find evidence for such amidst contemporary debate. After listening to Francis Blake's lecture in 1929 before the Vermont Medical Society about the transformation of nosology instituted through the division of pneumonia into its specific microbiological and immunological subcategories, a local practitioner would actually conclude:

> I want particularly to congratulate the Society on the papers presented, and I say it, having in mind, from my standpoint, Dr. Blake's paper. He served to emphasize that the clinical course of pneumonia especially runs parallel with the etiological diagnosis. That is that you can tell, from the clinical course of your case, without aid of the laboratory, what sort of pneumonia you have, if you are a fairly decent observer, and in view of the particular difficulties of laboratory diagnosis and country practice, it is a very valuable contribution. It served to emphasize, too, our helplessness, to any large extent, in any rational serum treatment.[86]

Nevertheless, at the same time that certain clinicians wore blinders, others sought to unite the various approaches to pneumonia. Russell Cecil, for example, was quick to uphold the continued use of physiology-based rationalism,[87] while others were hoping to find a means to transfer the Northeast urban hospital specifics to the small-town clinicians who were seemingly dependent, logistically, on the application of physiology-based rationalism.[88] In response to such concerns, a network of clinicians and public health workers would attempt to bridge the chasms—both logistical and epistemological—between the use of laboratory-based specifics in the hospital and physiology-based care in the home. Part II will address the evolution of this effort as manifested in the nationwide movement of state-supported pneumonia control programs, which would again transform the very conception of pneumonia—this time in the context of the evolving boundaries between private practice and public health.

The Massachusetts Experiment and New (York) Tensions

Before describing in detail the advent of the Massachusetts and New York efforts to transform pneumonia into a public health concern, it is useful to place such efforts in the context of the rapidly changing nature of antipneumococcal serotherapy itself. As Lloyd Felton's concentrated serum (either monovalent against types I or II pneumococci or bivalent) displaced its unconcentrated counterparts, some serum advocates remained focused on its efficacy. The serum treatment of type I pneumococcal pneumonia remained the standard-bearer, and as the field became more complex, its "spectacular" results would become ever more frequently cited as an incontrovertible gold standard.[1] Characteristic of type I testimonials was that presented by Harry Dowling: "It is not unusual to find that a patient who, the night before, was restless, delirious, dyspneic, cyanotic, and suffering intensely, appears on the morning following serum therapy, quiet, composed, rational, interested again in the world about him—in fact, very often, immersed in the pages of the morning newspaper."[2]

Much of the criticism of serotherapy, however, centered less on its efficacy than on its perceived impracticality and limited therapeutic range. In both of these respects, researchers soon produced powerful counter-responses. From the standpoint of practicality, pneumococcal typing—entailing the injection of a mouse's peritoneum with sputum and waiting eighteen to twenty-four hours for incubation before withdrawing the exudate for serological testing—had been both tedious and time-consuming. Particularly in the context of the need for early serum administration, several attempts had been made to speed the procedure.[3] By 1933, Albert Sabin (who would subsequently garner fame for the development of the oral polio vaccine) had introduced into the country what would come to be known as the "Neufeld test," reducing the time required to type pneumococci to fifteen minutes. Neufeld, the originator of pneumococcal typing (as described in

chapter 1), had in 1902 first labeled as the "quellung" (swelling) reaction the peripheral capsular swelling noted among individual pneumococci mixed with their corresponding type-specific antisera.[4] By the early 1930s, this seemingly academic finding had been transformed into a clinical test in Germany and England, and Sabin added his own critical innovations.[5] Essentially, flecks of sputum would be placed on cover slips with a wire loop, with a single type of diagnostic rabbit serum (instead of horse serum) and alkaline methylene blue dye added to each fleck. Within minutes, a clinician or technician using an oil-immersion lens would be able to identify the characteristic swelling, if present, thereby identifying the type of pneumococcus at hand. Dowling could thus by 1935 begin a presentation on serotherapy by offering that "physicians are, before all else, practical men," before discussing typing's feasibility and simplicity.[6] Typing had been transformed, ideally, into a bedside procedure.[7]

Regarding the expansion of serotherapy's range, it had been apparent to certain observers since the 1910s that the four types of pneumococci could be serologically further differentiated, though little impetus had been given to such studies in view of their perceived lack of therapeutic relevance. In 1927, however, Georgia Cooper, working for William H. Park at the New York City Department of Health (and funded to a large extent by Met Life's ongoing Influenza and Pneumonia Commission), began to investigate the subtyping of Group IV pneumococci (as the former type IV pneumococci had come to be termed) with the primary intention of specifically treating those afflicted by the emerging subtypes.[8] By 1929, she and her colleagues had split the group into ten types, against each of which they had developed monovalent antiserum; and by 1932, they had split the group into twenty-nine types, bringing the total roster to thirty-two, where it would remain throughout the decade.[9] Such expansion, when combined with the finding that many of the new types were prospectively found to be agents of disease in a general hospital setting, certainly represented the worst fears realized of critics of serotherapy's complexity.[10] Even Max Finland admitted that "the clinician faced by a group of thirty-two different strains of pneumococci is doubtless appalled."[11] But to those seeking the ever-finer mutual specificity of disease and therapy, serotherapy at least and at last had the potential to fulfill Cole's expectations: "Although the recognition of the multiplicity of types of pneumococci would seem at first to be confusing and to be of purely academic interest, it will, as a matter of fact, prove to be a simplification. It will become possible to recognize separate entities and to develop specific prophylaxis and therapy."[12] Applied immunology, as such, continued to blur the lines between academic and therapeutic interests.[13]

Thus, an ideal had been established: pre-made sera would be at hand for administration against all thirty-two types of pneumococci; a patient would arrive and produce the incriminating sputum; within fifteen minutes, the type would be identified; and the appropriate serum, once testing for allergic reactions had been performed, could be administered. Not everyone was pulling in unison toward this optimistically placed ideal, however.[14] Some clinicians, perhaps threatened by the emerging universal, specific approach to pneumonia, continued to voice their a priori concerns regarding the loss of physiology-based rationalism and the failure to account for regional disease variability. Concerning the former, a Tulane professor, as late as 1934, compared the pneumonia situation to the former typhoid situation (along diametrically opposed lines from which Cole had himself compared the two situations): "Until comparatively recent years, a constant effort was made to apply specific therapy to typhoid fever. When this was discontinued and instead of treating the disease we began to care for the patient, there was immediately an improvement as indicated by statistics. . . . Some of us may live to see most of our pneumonia patients managed in the same way."[15] Concerning persisting beliefs in regional variability, a former colleague (who had relocated to Texas) wrote to Maxwell Finland in 1934: "Wish you would have been here for the Southern Medical Convention a couple of weeks ago. The docs down here could stand some talks from you about the value of serum in pneumonia. From little I have been able to learn so far, they think the cases are so mild down here that they dont [*sic*] even bother to type the sputum: I doubt the mildness very much."[16]

Published dissent along such lines was becoming increasingly scarce, however, as the transformation of pneumonia as a nosological entity and of antipneumococcal serotherapy as an idealized specific continued in the wake of the Boston and New York developments. Simple indifference was instead more often the rule, and it is again difficult to chart precisely the extent of antipneumococcal antiserum's usage. From their academic bases, Leon Collins at the University of Pennsylvania commented on its "increasing" usage, and H. J. Moersch at the Mayo Clinic regarded it as "widely used."[17] However, Donald B. Armstrong, medical director of the Metropolitan Life Insurance Company, lamented in 1935 that only 5 percent of physicians in eastern communities (serum's supposed stronghold) appeared to be taking full advantage of available serum.[18] In the words of antipneumococcal serotherapy's increasingly confident proponents, such ignorance was itself becoming the object of criticism. Rhetorically, the history of serotherapy was reconstructed in tripartite fashion—with the dark ages of 1892 to 1913 followed by the academically interesting, if clinically murky, Cole-led Re-

naissance from 1913 to 1924, followed by post-Felton industrial modernity—both to absolve prior, and to condemn contemporary, ignorance.[19] One practitioner, recounting this history before the Tennessee Medical Association, would summarize: "Unfavorable experience with the previously used unconcentrated whole serum, fear of a severe reaction, nor indifference should keep one from acquainting himself with the value of specific serum therapy in pneumonia. . . . The use of anti-pneumococcic serum, particularly in Type I and II pneumonia, has passed the experimental stage and is a firmly established, acceptable procedure."[20] His discussant concurred that "we have all been asleep about the use of serum."[21]

Ignorance, moreover, was beginning to be translated into culpability, comparable to the negligent failure to apply two of the medical profession's most prominent procedures: the surgical removal of the appendix, and the treatment of diphtheria with antiserum.[22] At the level of the individual provider, this resulted in part from pneumonia's reconstitution—given the time-sensitive relation of serum administration to efficacy—as an *emergency,* as the monitoring and tinkering of physiology-based rationalism was to be superceded by the decisive use of serum.[23] But the critical roadblock to antipneumococcal serotherapy's wider dissemination—superseding the slowly resolving epistemological resistance to the specific—remained its cost. One Nebraska practitioner, after attempting to convince his county medical society of serum's benefits, nevertheless concluded that serum remained too expensive for "routine treatment."[24] In the wake of the Depression, this cost was difficult for most individual patients or practitioners to accept.

Yet to antipneumococcal antiserum's staunchest advocates, the failure of the community to provide the resources for serotherapy rendered it as culpable as the individual practitioner.[25] Indeed, by the early 1930s, Max Finland and his former colleague from Boston City Hospital, Wheelan Sutliff, would feel free to remark: "One difficulty has been discussed rather widely, the high cost of potent serum. . . . This therapy, however, is so valuable that the costs, whatever they are, must be met by appropriate authorities."[26] Finland and Sutliff, furthermore, were by that time not just armchair moralizing; rather, they had both been affiliated with the "Massachusetts Pneumonia Study and Service," initiated in 1931 as a dramatic "experiment" in resource distribution and the first attempt in this country to transform pneumonia into a public health concern.

The Massachusetts "Experiment"

Massachusetts had long been at the forefront of the nation's public health efforts, from the initial reporting of vital statistics by Lemuel Shattuck in the

1840s through the formation, in 1869, of the first state board of health with a widespread vision to improve the public's health.[27] By the advent of the twentieth century, the state's public health department had hitched its authority to the rising field of bacteriology and essentially restricted its domain to the control of contagious disease (through investigation, sanitation, and immunization), though pneumonia had remained largely beyond its purview.[28] But by the late 1920s, with such infectious diseases as typhoid and diphtheria on the decline, the public health department was in an expansive mood, even considering its role in controlling chronic diseases as well.[29] In this setting, pneumonia—the second-leading cause of death among infectious diseases in Massachusetts—was viewed at last as a legitimate public health concern by members of the department.[30]

Roderick Heffron, appointed the Massachusetts pneumonia study's field director, would later state his amazement that pneumonia's public health aspects hadn't long been apparent prima facie. As he remarked in the wake of the Depression: "Few if any diseases exact such a toll at the economic prime of life. It is therefore extremely fitting that in any consideration of public health some attention should be given to this disease. Yet almost without exception it has been completely neglected save for a passing remark of regret as to the futility of its control."[31] Indeed, little had changed from fifteen years earlier, when Francis Blake had bemoaned to Rufus Cole from an army camp amidst the influenza crisis: "If a case of meningitis, or scarlet fever, or diphtheria breaks out in a ward there is a great to do—the ward is immediately quarantined and everybody cultured. And yet all the meningitis, and scarlet fever, and diphtheria in the whole army doesn't amount to a row of pins compared to what the hemolytic streptococcus, or the pneumococcus for that matter has done in any cantonment in six weeks during this epidemic."[32]

In its actual origination, though, the attempt at the control of pneumonia had again followed that of diphtheria. The Massachusetts State Board of Health had first ventured from sanitation efforts toward a role in ensuring the application of therapeutic biologicals with its production and provision of free diphtheria antitoxin at the end of the nineteenth century.[33] Eugene Kelley (commissioner of the Department of Public Health from 1918–1925), and Benjamin White (director of the department's Division of Biological Laboratories) had years later apparently first discussed active control programs for diphtheria and pneumonia together, choosing diphtheria first because of its perceived urgency and better means of control.[34] The diphtheria program had consisted of an epidemiological study and an extensive health education program.[35] As such, as White would recall, it "showed the way for planning campaigns for the control of other communicable

diseases" through uniting a service provided to practitioners with a "study comprising theoretical and applied immunology, epidemiology, and clinical medicine."[36]

The Department of Public Health, meanwhile, in collaboration with Lloyd Felton himself, had been distributing its own concentrated antipneumococcal serum to selected hospitals since late 1928.[37] Mortality among the treated type I patients had been somewhat reduced, to 20.9 percent. And as Kelley's successor, George H. Bigelow, noted: "Another outcome of the hospital trials has been the awakened interest among members of the medical profession in the serum treatment of pneumonia. A demand has been created for the product, and its distribution could be greatly increased if we chose, or were able to release it for general use."[38] Expenses appeared prohibitive for a public health effort if antipneumococcal serum were to be given indiscriminately; but if the medical profession could be directed to treat only appropriate cases and to treat them early, then perhaps the department could reduce costs to the point of justifying public expenditure.[39] And given that far too many pneumonia patients admitted to hospitals were admitted late in the disease, a final critical element of the program was required: "placing antipneumococcic sera at the command of the local practitioner who sees his patient in the early stages of the disease."[40] Thus, the very data supporting serum's time-sensitive efficacy apparently necessitated a shift in the organization of pneumonia treatment—a shift that would occur against the backdrop of the previously cited tensions between hospital and home, laboratory and clinician.

On June 20, 1930, an informal pneumonia conference was convened, and a proposal drafted by White was soon sent to Bigelow.[41] One problem remained—finding who was to pay for the initial demonstration of the program's potential cost-effectiveness—and here White and Bigelow proved resourceful. If the program were constituted, not as a state function but as "a study [which] would be of value to physicians and pneumonia patients everywhere,"[42] then it appeared appropriate to appeal to one of the philanthropic foundations then playing such large roles in promoting public health efforts.[43] Bigelow wrote to the Commonwealth Fund in New York City and was granted $36,200 for one year (with funds to be distributed over four subsequent years, pending the results of the previous years' results).[44]

But what type of "study" should be conducted, given that type I serum's efficacy had apparently already been "proved"? It was to be a managerial and organizational "experiment" concerning the distribution of physical resources.[45] One way to cut the Gordian knot of debate between the serum treatment of pneu-

monia in the large city hospital and conservative treatment in the home was to see if serum treatment itself could be brought safely and effectively into the home and small community hospital. Bigelow would whimsically describe the entire program as an "adventure in decentralization."[46] As he elaborated: "The large majority of pneumonia cases are admitted to these hospitals on the fourth or fifth days of the disease, or later. For the people, then, to obtain the value inherent in this serum treatment it is necessary to make it available in the smaller hospitals of the State and in the homes of the patients. This means decentralization of service and constitutes a fascinating administrative experiment. Can this relatively complex diagnostic . . . and therapeutic service be decentralized without unduly impairing its quality?"[47]

By the winter of 1931–32, the program was in progress, with the following stated agenda:

> 1. To study the epidemiology of lobar pneumonia in the State. 2. To promote more prompt diagnosis of the disease. 3. To encourage and facilitate earlier and more general therapeutic use of concentrated serum. 4. To study and improve methods for serum production. 5. To correlate the studies on serum production with the results following its clinical use. 6. To devise procedures for the future prevention, serum treatment and control of the disease.[48]

Ten areas beyond Boston (which itself included eight participating hospitals) were first chosen, based not on geographic distribution (though they extended across the state) but on the range of organizational problematics they posed.[49] Still in the pre-Neufeld test era, each of these areas was given its own (concentrated bivalent types I and II) serum supply and laboratory for performing sputum typing for local physicians, with technicians first sent to Boston City Hospital to perfect their typing skills. Moreover, intensive statewide education was initiated, with a variety of "media used to spread this propaganda": from intensive full-day courses, to meetings in local towns and among district medical societies, to the distribution of thousands of flyers and reprints (including the mailing of Bigelow's presentation of the program before the Massachusetts Medical Society to every physician in the state).[50]

By the end of 1932, the program was already being hailed as a success by its originators. Four additional areas had been added, with eleven others requesting inclusion (through their local physicians, hospitals, or boards of health).[51] Serum distribution had nearly doubled over the previous year, reflecting the impact of the educational program.[52] With a progressivism that belied their own earlier analysis, the program's proponents wrote the Commonwealth Fund administra-

tors: "Physicians at large throughout the State have already or are rapidly becoming cognizant of the fact that something can be and is being done for lobar pneumonia. The interest awakened by this study is leading to an increased demand for pneumococcus typing, for serum and for information bearing on pneumonia, and is readily observable when the question of pneumonia is brought up in the meetings of the various medical societies of the State. Such interest as is now apparent is a distinct contrast to the obvious lack of it during the initial months of the work of this study."[53]

To the necessary question—did the "decentralized" administration of serotherapy actually work for the individual patient?—Heffron offered a resounding affirmative. Among 188 patients with type I pneumonia treated by 1933 within the first four days of illness, only 10.6 percent had died, comparing favorably not only with the 25.9 percent mortality found among 349 incidentally untreated patients with type I pneumonia but with Cole's benchmark Rockefeller success as well.[54] By the end of 1933, Heffron could congratulate himself on the nearly fourfold increase in demand for pneumococcal typing and serum distribution as well as on finding himself in the situation that "if serum were to be distributed without restriction to all physicians desiring it, our total present budget would undoubtedly be insufficient to finance its production."[55]

But the clause "without restriction" referred not only to the volume but also to the manner of serum distribution: while the program's goal was decentralization, its initial manifestation looked suspiciously centralized. Seemingly generous concessions had been made. Whereas the program's initial Advisory Committee, for example, had neglected to include any general practitioners, two were added in late 1930.[56] The chief concern of local general practitioners, though, hinged on the usage in each area of two or more physician "collaborators" as the designated representatives of the state effort. Initially, in order to administer serum, a practitioner would have to call the local collaborator, who would confirm the diagnosis, obtain blood cultures and facilitate typing of the sputum, and either administer the serum directly or give the practitioner the appropriate serum (itself free of charge) to treat the patient "under competent guidance."[57] Heffron noted that "the only thing we ask in return for the serum so distributed is a case record properly filled out for each patient so treated."[58] What he more blithely hinted at was that the collaborator was permitted to charge the patient a usual consultation fee—hardly ameliorated, in the eyes of local practitioners, by the Commonwealth Fund's willingness to pay for such services if the patient could not afford to do so.[59]

Early grumblings by practitioners regarding the usurpation of their authority and earnings by the collaborators developed into an emerging stand against the

encroachment of public health into a formerly private disease.[60] From the center, Heffron and Gaylord Anderson (deputy commissioner of the Department of Public Health) would refer to the public/private dynamics as epitomizing "a properly balanced public health program."[61] The "local" origin of the consultants had seemed to parallel the usage of local hospitals, laboratories, nurses, and physicians themselves in the program, rendering "each community an organized self-contained unit."[62] But from the beginning, Heffron had recognized the need to justify such encroachment to the profession at large, used to having "antipneumococcic serum [provided] to all practitioners who requested it in and around Boston."[63] Heffron politely blamed the Commonwealth Fund for having "forced" the public health department to obtain a return on its investment through more careful serum distribution,[64] and the emerging peripheral resistance of the practitioners first became apparent to the Commonwealth Fund's administrators themselves by August of 1933.

Committed to a centralized program, the Fund's administrators warily noted of their beneficiaries: "There has been, as was expected, a reluctance on the part of the practitioners to call in the consultants and [the directors of the program] are inclined to believe that if the laboratories will offer the serum to any physician, there may be a better distribution and more cooperation."[65] By this time, several factors—from the success of physician education and the coincident advent of the Neufeld method of typing, to the request by the Commonwealth Fund that the state assume more of the financial burden of the program—had united to undermine, for Bigelow and Heffron, the necessity of the expensive collaborators.[66] The key factor, however, remained the wedge local practitioners proclaimed had been driven by the state between themselves and their patients. While Heffron at the time had cited the "very successful" relationship thus engendered,[67] in his final tabulation of the program, he would admit: "In some respects this was a precarious system, and much depended on the local situation, medical and otherwise, and the popularity, quality, and integrity of the physicians designated as collaborators. . . . In some instances other physicians feared losing their patients to the collaborator called."[68] Moreover, such hesitation to seek a consultation was a deterrent to serum administration; and if the extent of such administration was one of the chief outcomes of a study in decentralization, then the consultants were a hindrance to the success of the study itself. Since only 10 percent of all type I and II cases were estimated to have been treated under the collaborator system, concluded Heffron, "the collaborator system might possibly be regarded as only 10 percent effective."[69]

Thus, by the time Heffron submitted his proposal for 1934–35, the limits of

public health encroachment on private practice were becoming apparent. Placing a positive, evolutionary spin on the process, he would recount that while the early use of the consultants had been essential to the completion of the "study" aspects of the program, the service aspects of the program now demanded that "in the eyes of the State which licenses the physicians, all must be considered alike."[70] More pragmatically, he confessed: "Many physicians will not call a local consultant, feeling that to do so will tend to belittle themselves in the eyes of the patient. To continue to distribute the serum solely through a group of consultants would then be to limit the use of the serum in such a fashion as to defeat the main purpose of its distribution. It would furthermore stimulate a growing resentment among the medical profession."[71]

For an alternative model, he would this time turn to another public health effort, namely, that concerning infantile paralysis. In the case of suspected polio, any physician could administer state-provided convalescent serum to a preparalytic patient—provided one had first performed a lumbar puncture and demonstrated spinal fluid characteristic of the disease. As an analog, any physician who obtained a positive type I or II sample within the first four days since the onset of a case of pneumonia could receive serum free of charge from the state.[72] The plan was attempted on a trial basis in Newton in 1933, and by the end of 1935 the collaborator system had been dismantled.[73]

By the end of 1935 the commitment from the Commonwealth Fund had itself come to an end, and the state was ready to assume full responsibility for the pneumonia program. To the public health department, the "experiment" in distribution appeared to be a success and, more importantly, a harbinger of potentially more extensive efforts nationwide. Despite persisting limits to serum utilization, nearly one thousand patients had been treated by nearly four hundred physicians in ninety-eight towns and eighty hospitals.[74] Twenty-two percent of the patients had been treated at home.[75] Type I mortality in particular remained at 11.1 percent overall when serum was administered within the first four days of illness and was reduced to 8.3 percent for such patients between the ages of 10 and 49 (comprising 83 percent of all type I patients).[76] Four serum-related deaths had been identified—one from an anaphylactic reaction and three from "chill" reactions (which were deemed to have been eliminated from serotherapy by the end of the study)—demonstrating the relative safety that would accompany such efficacy.

In what was to become a widely repeated exercise, Heffron concluded by calculating that if the benefits of types I and II antipneumococcal serotherapy were to be extended nationwide, more than 18,000 fatalities per year could be

avoided.[77] Pneumonia efforts in Massachusetts would have an impressive national impact;[78] indeed, a West Virginia clinician would remark in the ensuing years that the "outstanding" Massachusetts program had commanded "worldwide attention."[79] Nevertheless, the shift in the public/private dynamics entailed was already apparent by the end of the Commonwealth Fund's involvement in the Massachusetts program, for private practitioners were glad to accept free typing and serum—without the intrusion of state direction. Such intimations of resistance, moreover, would become glaringly apparent by the time the Commonwealth Fund, in 1935, turned to the state of New York for a confirmatory study of pneumonia control.

Control, Indeed

New York was certainly a logical location for a "pneumonia control program," as it would come to be called.[80] From the groundbreaking studies of the Rockefeller Institute and the efforts of New York City's and the state's departments of health at serum refinement over the previous two decades, to the financial backing of the Metropolitan Life Insurance Company and the Commonwealth Fund, a mutually intertwined—if not always united[81]—clustering of interests had long been at the vanguard of antipneumococcal serotherapy.[82] Type I serum had been distributed free of charge by the state since 1916, and pneumonia had been a reportable disease since 1918.[83] But when the members of such groups finally attempted to launch a centrally administered pneumonia control program in 1935, they would find themselves beholden to a defensive medical profession that was loathe to yield control over the treatment of its patients.

The actual formation of the New York State Pneumonia Control Program entailed the input of a diversity of interests. Already in 1931, Met Life's Donald Armstrong had written to the Commonwealth Fund regarding the logistics of the Massachusetts program.[84] And by early 1934, representatives of the state laboratories had themselves expressed an interest in pneumonia control to Thomas Parran, the commissioner of the State Department of Health.[85] Events began to take form in late 1934, when Armstrong and Met Life's assistant medical director, A. J. Lanza, appealed to the State Medical Society to further the usage of Met Life's free nursing service for pneumonia patients.[86] In response, the society's chairman of the committee on public health and education proposed to extend the program to include the increased use of serotherapy as well; and a medical society subcommittee on pneumonia control was created, with antipneumococcal serotherapy champion Russell Cecil as its chairman.

By February of 1935, representatives of the state's division of laboratories and research had asked Parran for increased funding for the provision of serotherapy in general, while at the same time state medical society representatives asked Parran for an increase in antipneumococcal serotherapy production in particular.[87] Through Parran's intercession, his longtime friend Governor Herbert Lehman soon approved a twenty-thousand-dollar appropriation for increased serum production.[88] By April, Donald Armstrong discussed with Parran the possibility of uniting the State Medical Society's pneumonia control efforts with those of the State Department of Health;[89] and after discussion with his public health colleagues, Parran assented, attempting to cement an admittedly "complicated" union between the State Medical Society and the State Department of Health by having the Commonwealth Fund and Met Life support the program through matching contributions.[90] By the end of 1935, the Advisory Committee of the New York State Pneumonia Control Program had been formed and was formulating policy—with the medical society's Cecil as its chairman.[91]

The New York program held inherent advantages over its Massachusetts counterpart, including tight control over an extensive network of laboratory facilities (except those in New York City) and serum distribution centers.[92] The campaign was launched in January of 1936 with great fanfare, including a telling three-way radio discussion among Governor Lehman, Parran, and State Medical Society president, Frederic E. Sondern.[93] Parran again reformulated pneumonia as a public health crisis: "This disease causes a loss of 12,000 lives in New York State each year—a number equal to the entire population of a good-sized city—Tonawanda, for example; or Beacon, or Fulton, or Oneonta. If each year such a city were to be destroyed by some strange, new plague, we would think no cost too great, and no effort enough to put an end to such loss of life!"[94] Sondern concurred, again drawing on diphtheria for comparison: "You may remember, Governor, how the State Medical Society and the State Department of Health, with the aid of interested citizens, organized the drive against diphtheria ten years ago. Today, diphtheria has almost disappeared in many parts of the State."[95] But it was to be clear from the discussion that of such involved parties, "greatest of all is the contribution of the State Medical Society."[96]

By August of 1936, the State Department of Health could report a 36 percent increase in the number of diagnostic laboratory facilities and a threefold increase in serum production. The state's educational committee, moreover, had generated a sixteen-page pamphlet on pneumonia diagnosis and treatment, distributed to every physician in the state, as well as radio publicity and traveling visual exhibits.[97] By the following year they would add two technical motion pictures and

five Graduate Institutes on Pneumonia, full-day courses attended by approximately 730 physicians.[98] New York had thus taken on the responsibility of transforming pneumonia into a public health concern as enthusiastically as had Massachusetts.[99]

Nevertheless, whereas the limits of the Massachusetts program had perhaps opaquely illustrated the tensions felt by private practitioners as the state attempted to redefine the boundaries of public health, those of the New York program would starkly depict such tensions let loose. As members of both the public health department and the Commonwealth Fund realized: "The State Medical Society regard the pneumonia program as their own, and rightly, I think, take the attitude that they are using the State Department of Health and other organizations as agencies to carry out their own plans."[100] To the leaders of the State Medical Society, however, such cynicism failed to recognize the "natural" domain of the state's private physicians and their expected primacy in guiding not only the care of individual patients but collective efforts at the population level as well.[101] In his recounting of the evolution of the pneumonia control program, Peter Irving (secretary of the State Medical Society) characterized the chain of responsibility as clearly extending from the private practitioner's concern over public health issues, to the State Medical Society, and through them, to the public health department as a means to the society's ends:

> When the call comes from the physicians of a state through their society's administration, it is tantamount to a guaranty [*sic*] of a closer and more intimate relationship with the health department than can be obtained in any other way. The membership will be under moral obligation to meet health officers on an even basis. Moreover, physicians look naturally to their county and state society officials for aid in their work when it has a public health bearing or requires graduate medical education, and such a program implies both. Once undertaken, a state pneumonia control program is *ipso facto* a state department of health activity. It is, however, one which calls for continued and continuous active participation by the state medical society."[102]

The program may have been a State Department of Health activity *ipso facto,* but it apparently remained the duty of the profession to prevent it from becoming the state's program in practice.

Such vigorous boundary protection was only one specific component of the medical profession's general attempts, throughout the 1930s, to protect itself against the perceived threat of government intrusion.[103] To contemporary physicians, though, it also served as a microcosm of this larger struggle. By late 1936 Floyd Winslow, president of New York's State Medical Society, would use his plat-

form concerning the pneumonia control program to launch into an expansive critique of government encroachment. He began by proudly describing his medical society's extension of its efforts into such established and emerging public health concerns as "pneumonia control, cancer, syphilis, maternal welfare, child hygiene, and nursing education."[104] As Winslow turned to the pneumonia control program in particular, though, he made it apparent that the State Medical Society's hold on such gains remained tenuous, requiring further vigilance and advancement: "During the winter it is likely that each county medical society will be requested to designate a member to speak on the radio or at public meetings on this subject [of pneumonia control]. May I urge you to accept this responsibility as a way still further to place the organized medical profession in the position of leadership in public health activities."[105] When generalized to the larger debate concerning the relationship between private and state medicine, the stakes were high: it was to be a battle between those private practitioners "required to give our very best to every patient, or lose out in the gentlemanly competition which exists within our ranks," and those merely aspiring to "an assured income under bureaucratic control where our highest ambition is more likely to be to keep ourselves solid with the politicians who have taken over the job of running our profession."[106] The logistics of the pneumonia control program would thus assume a symbolic importance representative of the very tensions between the American medical profession and the forces it perceived to be delimiting its developing hegemony.

Thomas Parran left New York in April of 1936 to become surgeon general of the U.S. Public Health Service, taking with him lessons regarding pneumonia control that would have national ramifications (to be discussed in chapter 5).[107] More locally, the New York medical profession was becoming a nuchal nuisance for those in favor of centralized state control—and in particular for the Commonwealth Fund, whose administrators now clearly split in their musings between the wonderfully cooperative Massachusetts gentlemen and the gang from New York.[108] Unhappy with issues ranging from the absence of collaborators in the New York program to difficulties in retrieving case reports, the Fund's administrators saved their ire for a debate over the necessity of diagnostic typing; and while the debate would be technically "won" by the Commonwealth Fund, its subtext, on the eve of the nationwide emergence of state pneumonia control programs in the mold of the Massachusetts and New York programs, would expose the ultimate restrictions on state administrators vis-à-vis the private practice of treating pneumonia.

The Advisory Committee, on December 20, 1935, had made typing a prerequisite to the administration of type 1 serum (through 1936, the only serum sup-

plied).[109] By the following spring, though, it was becoming apparent to the Commonwealth Fund administrators that despite the fact that local physicians were failing to type sputum in many instances, such physicians continued to receive serum.[110] Many physicians had been treating their patients as such with serum for nearly twenty years, and the State Medical Society did not wish to "adhere . . . too rigidly to absolute standards in order to preserve the physician-patient relationship."[111] What was as much at stake as the doctor-patient relationship, however, was the state-physician relationship, that is, avoiding "the possibility of antagonizing practitioners throughout the state by withholding from them the service they have been accustomed to having."[112] After all, it appeared that such compromise worked to everyone's benefit. Declared the assistant commissioner of health: "A highly important by-product of the pneumonia control program has been the strengthening of the relationship between the State Department of Health and the medical profession. . . . Physicians in private practice seem to feel quite generally that, as far as pneumonia is concerned, something definite is being done for them."[113]

For the Commonwealth Fund administrators, however, the happiness of the entitled practitioners was of less concern than were the means of *changing* such physician attitudes.[114] They dichotomized such potential means into the "regulative" versus the "educational"—and sided with the former.[115] After failing in the fall of 1936 to force the issue through threatening to withhold funds, the Fund's administrators would succeed through such coercion the following year.[116] Their victory, however, represented a brief last thrust at the New York Committee. By the spring of 1937, pneumonia control had become still more of a political favorite, as the New York legislature appropriated $400,000 for the supply of free serum.[117] Such an appropriation at last obviated the need—when the funds would ensue the following year—for the Commonwealth Fund's largesse and its attached strings.

By March of 1938, such frayed ties would be severed. Moreover, by this time, given the advent of satisfactory concentrated monovalent serum for multiple types of pneumonia, practitioners themselves had come to understand and accept the need for a priori typing to guide their therapy. As such, the "educative" principle advocated by the State Medical Society had definitively won out over the "regulative" principle adopted by the Commonwealth Fund administrators. And as state pneumonia control programs began to sprout across the nation, it became established that private practitioners were to be enhanced by new tools placed at their disposal rather than superseded by consultants—or curtailed by restrictions—introduced by the state.[118]

The New Standard, the New Deal, and the Pneumonia Control Programs

By the late 1930s, many of the tensions exposed and further engendered by antipneumococcal serotherapy over the previous two decades (as discussed in chapter 3) seemed to be resolving in the wake of contingent technological improvements on the one hand, and a continued therapeutic reorientation toward the use and evaluation of the specific in medicine on the other. Yet as discussed in chapter 4, the *application* of such an expensive, labor-intensive specific as antipneumococcal serotherapy would by this time create a new set of tensions, which at the national level would evolve amid the competing influences of the attempted ascendance of the United States Public Health System (in the setting of the New Deal and the emerging suggestion of health care as a fundamental right), versus the decided ascendance of an organized medical profession championing the cause of the autonomous practitioner. This chapter explores the technological and professional context of pneumonia's reconstitution as a national public health concern in the late 1930s on the basis of the exigencies of antipneumococcal serotherapy, in the form of a nationwide proliferation of state pneumonia control programs and on the eve of the chemotherapeutic antimicrobial "revolution" itself.

The New Standard

Antipneumococcal serotherapy was widely considered a powerful tool for the practitioner by this time. Continuing the trend begun earlier in the decade and buoyed by the apparent successes of the Massachusetts and New York state programs, serotherapy would garner further support to the point of being considered "the standard procedure by all investigators in the field" for the treatment of pneumococcal pneumonia, a triumphant specific mandating that the practitioner employ it—and the community pay for it.[1] Again, the treatment of type I pneumo-

coccal pneumonia served as the standard of efficacy. Russell Cecil, resplendent with the success of the New York program, could again edit the history of the field, claiming: "I cannot recall a single skeptical article since the introduction of Felton's concentrated serum."[2] Lending further urgency to the early recognition of the symptoms of pneumonia and the prompt administration of serum, he would report a 5 percent overall mortality among patients suffering from type I pneumonia treated within twenty-four hours of the onset of disease.[3] No longer satisfied with relative reductions in mortality, Cecil could advance a cure.[4] Still more dramatically, a group at Cincinnati General Hospital reported that not a single type I pneumococcal pneumonia patient had died among fifty treated with monovalent serum "early and adequately."[5] A failed treatment thus implied improper typing or a preexisting complication.[6]

Parallel with the deepening of confidence in the established type I and II sera came the realized expansion of serotherapy's range as well. By 1937, Jesse Bullowa could report before the California Medical Association that sera for types V, VII, VIII, XIV, and XVIII pneumococci were already as effective as that for type I.[7] It appeared that before long similar results would be extended against all thirty-two types of pneumococcal pneumonia.[8] Moreover, by 1937 such efficacy and range were enhanced yet again through the discovery at both the Rockefeller Institute and the Lederle Laboratories that rabbits could be successfully substituted for horses in the production of monovalent therapeutic antisera.[9] The Rockefeller team soon reported that rabbit serum could be generated far more cheaply than horse serum and could be administered as a single curative dose in the majority of cases with an apparent further reduction in the number of untoward reactions.[10] Within a year, they would further detail the successful use of such monovalent serum against nine types of pneumococci, with a combined mortality of 3.4 percent when cases of the ever-tenacious type III pneumococci were excluded from the analysis.[11]

By the late 1930s, with the dramatic rise of the antipneumococcal sulfa drugs still on the therapeutic horizon (sulfapyridine would be introduced in America during the 1938–39 winter pneumonia season, as will be extensively detailed in chapter 6), the treatment of pneumonia with type-specific antiserum could be cited as one of medicine's crowning achievements.[12] Hailed as a therapeutic "revolution,"[13] it was explicitly compared to such contemporary scientific achievements as the treatment of diphtheria with antitoxin, diabetes with insulin, and pernicious anemia with liver extract.[14] Even in view of such epochal discoveries, one Texas clinician remarked before his state medical association in 1937 that "in the annals of clinical medicine, no more brilliant chapter is to be found than the

one detailing the development of the specific serum therapy of pneumococcic pneumonia."[15] Describing the triumphant union between the lab and the clinic through the language of contemporary racial hygiene, he continued: "Serum therapy may well be called the eugenic child of modern clinical medicine, representing the fruition of the mating of pure science with clinical medicine."[16]

Once again, not only had William Welch's denial of a specific for pneumonia been refuted, but the scripture of Osler himself was to be revised. This could take a reverential turn, as when Peter Irving reflected: "If Sir William Osler were alive today, he would be deeply gratified to have seen medical knowledge advance so that he could radically revise his dictum phrased before typing of the pneumococcus was known. No doubt he would have been one of the first to have said that pneumonia can now be cut short by early use of enough specific serum."[17] Or it could take a more critical form as an implied further relegation to adjunctive treatment of physiology-based rationalism and a rejection of the faith in the *vis medicatrix naturae* characterizing Osler's generation:

> Only a few years ago when discussing this subject we devoted most of our attention to the details of good nursing care and proper methods of symptomatic treatment. We concerned ourselves with such subjects as the proper temperature and the ventilation of the sick room, the relief of tympanites, the administration of digitalis, and the use of oxygen. We followed the footsteps of Osler, who said: "It is a self-limited disease and runs its course uninfluenced in any way by medicine. It can be neither aborted, nor cut short by any known means at our disposal." In these later years, we have come to a little better understanding of the subject. New and potent therapeutic weapons have been placed at our disposal.[18]

Indeed, Osler's Captain of the Men of Death was to be cut down by the arsenal provided by science to the modern clinician.

Certain physicians did—for good reason—remain wary, lest physiology-based rationalism and the treatment of the patient per se become lost in the application of the modern specific.[19] However, such voices were becoming dimmer. Instead, while a New Hampshire practitioner would refrain from calling for the "abandonment of the older, well-established methods of symptomatically treating lobar pneumonia," he nevertheless chose to emphasize the need for "the more widespread adoption of the newer and more specific methods of treating this disease in general practice."[20] At the same time, implicit in such calls to general practitioners was the growing expectation that regionalism and personal preference were to succumb to the authority of "controlled" clinical trials.[21] Clinical impressions were to give way to scientific—and hence, universal—truths.[22] As a Vir-

ginia practitioner would summarize: "Today the administration of the serum is not a whim of the doctor but a direct obligation which he owes the patient, who entrusts his life and welfare in the doctor's hands."[23]

Resolving in the context of such universalism—and in the wake of the Massachusetts and New York findings that serum could be administered in any locale—was the formerly tempestuous debate concerning home versus hospital treatment of pneumonia patients. While isolated holdouts would continue to advocate for one or the other,[24] a pragmatic calculus was emerging: rather than relying on absolute mandates, the clinician was to weigh carefully such considerations as the relative capacity with which a patient's home could be equipped with the diagnostic and therapeutic amenities of the hospital versus the relative speed and safety with which a patient could be transported to a hospital.[25] Instead, the moral fervor of such previous aspects of the debate was subordinated to an increasingly conventional conviction: that pneumonia was to be construed as the medical equivalent of the surgical appendix, a treatable emergency, the mortality of which "increases rapidly with each hour of delay in giving serum."[26] Just as the surgeon's skills and scalpel were weighted with responsibility, so was the medical physician's preparedness to administer serum. As one West Virginia practitioner asserted:

> Nothing in the experience of any physician can be more dramatic, or more gratifying than the response of a patient who is very sick with lobar pneumonia to proper serum therapy. This new therapeutic agent places a very serious responsibility upon the shoulders of the practicing physician. He has no moral right to diagnose, prescribe, and say he will be back to see the patient the next day. It is incumbent upon the physician to remain on the case practically continuously, or to arrange for another physician to do so, until all the available facilities for adequate serum therapy have been exhausted or until the patient has shown a satisfactory response to treatment.[27]

Moreover, serum's supporters demanded that such individual physician responsibility be paralleled at the hospital level by preferential and immediate admission of pneumococcal pneumonia patients at any time of day (as in acute surgical cases), and, critically, at the community level by the provision of free serum, along the lines suggested by the Massachusetts and New York pneumonia control programs.[28]

Pneumonia in the Wake of the New Deal

These demands were not insignificant, however, given the costs of treating pneumonia in general, and with serum in particular.[29] When the Committee on the Costs of Medical Care had conducted its survey of the costs of illness, the average cost of treating a case of pneumonia from 1928 to 1931 had been $58.72;[30] when the Metropolitan Life Insurance Company performed a similar study of a more urban sample in 1930–31, the cost was found to be $98.03—in the absence of serotherapy.[31] By 1938, Joseph Hirsh, working for the Committee on Research in Medical Economics in New York, could report on the costs of treating pneumonia in New York City for the preceding three years. In the context of a median yearly household income of $1,500.00, the median cost incurred by a case of pneumonia had risen to $134.16, while the average cost had risen to $167.60.[32] Serotherapy—at $7–17 per 25,000-unit infusion—had accounted for 16.3 percent of the overall cost of treating pneumonia, but the extent of the expense had been quite setting-dependant. On the private wards (where it was used in only 16 percent of the cases) it had run to only 4.5 percent of the total bill, while on the public wards (where it was used in nearly half the cases) it had run to 23.5 percent.[33] In nearly one-quarter of the cases in which it had been used, moreover, serum expenses made up over half of the final tally; and as serotherapy continued to be increasingly used, such cumulative costs could only be expected to rise.

Private insurance to cover even hospitalization remained rare at this time (with less than 7 percent of the population covered by 1939), while national health insurance (to be discussed shortly) remained the loathed target of the very New York State Medical Society leaders advocating serum so strongly.[34] Thus, substantial economic disincentives could tempt both sick pneumonia patients to avoid their physicians and conflicted physicians to avoid the use of serotherapy. Bemoaned one Tennessee physician: "In the days of depression when people are trying to save even on doctors' bills, we are frequently not called to see cases of pneumonia as early as we would like. They postpone calling us, hoping that it is not pneumonia, and so we do not often see the cases early, especially on the first day."[35] And a Kentucky practitioner, acutely aware of the larger economic forces at play, responded with caution to a presentation on serotherapy's benefits: "[The] excellent presentation of this valuable, scientific treatment is of value only to those persons able to pay for its average cost, $140.00. . . . There is no question whatsoever about the value of this particular treatment of pneumonia, if given by physicians who have been sufficiently trained in the technique of its administra-

tion, but it will require a long time and millions of dollars to make it generally available to all who are afflicted with this, one of the most serious of diseases."[36]

Indeed, the universally applicable specific remained far from universally applied: the University of Cincinnati's Marion Blankenhorn, a strong serotherapy advocate, calculated in 1938 that during the previous year, only 21 percent of type I and II pneumococcal pneumonia cases in the United States had been serum-treated.[37] And a survey by the U.S. Public Health Service's Kenneth McGill of typing facilities throughout the country found strong regional variation, with the Southwest and Southeast in particular lacking in facilities.[38]

While physician ignorance regarding the utility of antipneumococcal serotherapy remained a contributing factor to such limitations,[39] the financial hurdle appeared the more significant factor to contemporary observers.[40] Yet with a new standard of pneumonia care emerging, proponents of serotherapy were increasingly unwilling to excuse such cries of poverty. In the midst of a profession and society increasingly concerned with the costs of medical care and "the money value of a man" (i.e., a worker saved from an invalid state or death), serotherapy's advocates invoked a pragmatic calculus of costs and benefits to justify its universal application and funding.[41] Alvin Price, in Detroit, had in 1935 first drawn attention to the possibility that the expense of serotherapy could be ameliorated by the savings realized through a reduction in the duration of treatment (and its attendant nursing care, oxygen treatment, etc.).[42] Within two years, such claims for cost amelioration would be transformed into claims for actual net cost savings (with a bit of moralizing thrown in for good measure): "The longer one waits, the more it is going to cost, and the longer one hesitates about giving serum the longer the illness is going to be, the more money will have to be spent for hospital days care or for special nurses, and one may not have the patient in the end."[43]

More radically, certain advocates would extend such a cost-benefit analysis beyond treatment costs to the general "value" of patients themselves. Bullowa, for example, would cite a $2,500 annual male wage in calculating that saving the lives of the 809 men who died of pneumonia in New York City in 1935 would have saved the city approximately $20 million in future earnings.[44] The most extensive and expressive such demonstration was offered by Millard Knowlton, director of the Bureau of Preventable Diseases of Connecticut's State Department of Health, at a meeting of the Connecticut Public Health Association in December of 1937 in which he lamented the inadequate funding available to his state's public health department for an expansion of its own pneumonia control program. After comparing the pneumonia patient dying amidst a commercial sea of serum to Coleridge's parched Ancient Mariner, he asked his readers to calculate "the

gamble of life without pneumonia serum."[45] An expenditure of $118,400 for the provision of serum to cover each type of pneumococcal pneumonia for all of Connecticut's citizenry would entail a per capita cost of 6.7 cents per year. When measured against the 6.6 cents per capita spent by New York with its $400,000 serum outlay, Knowlton would inveigh: "What good Connecticut Yankee would object to going New York State a fraction of a mill better on a life-saving program?"[46] Moreover, if the average life lost would represent ten thousand dollars in lost wages (conservatively combining the lost lives of both men and women), then the yearly toll of Connecticut's 715 pneumonia deaths would represent approximately $7 million in "population assets." The expenditure of $160,000 (combining serum, laboratory, and administrative costs) to save four hundred lives would thus "cost" four hundred dollars to save each life "worth" ten thousand dollars in future earnings: "The value of a life saved would be 25 times the cost of saving it."[47] For still others, though, even such utilitarian calculi would yield to the absolute moral stance that no patient should be denied a lifesaving measure, which "is apt to be quite expensive but after all this may be met by a shorter duration of the disease thereby effecting a reduction in hospital expenses and at all events is cheaper than a funeral."[48] Either way, the message was clear: it was the mutually reinforcing economic *and* moral duty of the nation's public health departments to establish well-funded control programs against what had become the leading cause of death among infectious diseases in the country.[49]

This would become the rallying point of a network of researchers, clinicians, and public health administrators, who, having fostered or been inspired by the successes of the Massachusetts and New York pneumonia public health "experiments," hoped to make available the wonders of antipneumococcal serotherapy to the nation's populace at large. Again, this effort would be grounded in an economic framework strengthened in the wake of the Depression: "Forty percent of the total number of pneumonia deaths are of men and women in the most economically productive period of life, those from 15 to 64 years of age, their deaths robbing families of breadwinners, industry of producers, and communities of consumers. The responsibility for the care of many of the cases falls upon the community, since many individuals find the treatment of pneumonia too expensive to bear."[50]

However, as delineated by the director of New York's pneumonia control program before the annual meeting of the Ohio State Medical Association in 1936, money and efficacious specifics were not enough. Public health infrastructure needed to be developed for the administration of such programs, and the population at large needed to be educated (presumably, after physicians had already

been so trained) regarding the urgency and ease of using such a program to treat pneumonia as early in its course as possible.[51] Thus, while Cecil's colleague Norman Plummer could declare before the American Medical Association in 1938 that the "greatest advance in the past few years" regarding the treatment of pneumonia had been its emerging transformation into a public health concern, the potential realization of such an agenda in its entirety—the closing of the "great gap" between the possible and the actual in the implementation of pneumonia control—remained the chief challenge to such individuals as Rufus Cole, Russell Cecil, and the Met Life administrators who had battled the pneumococcus for decades.[52] Indeed, as Cole remarked of pneumonia control at the time: "In view of the multitude of organized campaigns now under way to control tuberculosis, diphtheria, cancer, venereal diseases and other specific ills, one hesitates to suggest that public health authorities gird their loins for still another battle. And yet the experience of the last 20 years strongly indicates that the medical profession alone, unaided by public health organizations and unsupported by public opinion, can never make an important impression on the prevalence of, or mortality from this group of diseases."[53] For all of Cole's former emphasis on the specific interaction between antibody and microbe, the role of the community now seemed vital to the defeat of the pneumococcus.

In this "battle," Cole and his contemporaries would have a powerful ally: Thomas Parran, Roosevelt's surgeon general and the former coordinator of New York's own pneumonia control program. To place Parran's own ethos regarding the emerging role of the public health system—and in particular its application to the attack on pneumonia—in context, it is first necessary to situate it among the post-Depression debates in America concerning the propriety of governmental incursion into health care. During the formulation of the New Deal from 1933 to 1935, a group of reformers had attempted to include compulsory health insurance within Roosevelt's proposed Social Security Program; yet Roosevelt, opposed by a unified and conservative American Medical Association in this respect, and fearful of jeopardizing his larger program, had allowed compulsory health insurance to fall off the agenda and out of the Social Security Act as passed in 1935.[54] Such was a forerunner of events to take place throughout the remainder of the decade.

By the late 1930s, emboldened by perceived public enthusiasm for limited governmental encroachment into health care delivery and the care of the indigent, the reformers—including leaders of the Social Security Board, the Children's Bureau, and Parran's U.S. Public Health Service—would again attempt to formulate an expansion of the federal government's role in health care delivery and in-

surance.[55] In 1937 plans for a National Health Program—whose proposals ranged from the expansion of public health services and federal hospital construction in indigent areas to the possibility of compulsory health and disability insurance—were formulated and thereafter announced at a National Health Conference convened in Washington, D.C., in July of 1938.[56] However, in approaching how to expand care to the indigent, the reformers were themselves divided. Some members championed compulsory health insurance, while others—including, by this time, Parran—instead hoped to use federal money and agencies (in Parran's case, the U.S. Public Health Service) to support state and local efforts to provide such care. In this respect, Parran was closer to promulgating the ethos advanced by the AMA than that of his more radical reforming colleagues, just as the AMA's leaders—fiercely opposed to compulsory health insurance in particular—were compromising to some degree in moving to espouse just such an expansion of federal assistance, determined and administered by local agencies (especially, in their case, the state medical societies).[57]

As a broad movement, the National Health Program was a political failure, a victim of a divided front among the reformers in the face of the more unified lobbying of the AMA as well as of Roosevelt's lack of interest in making health care reform (and particularly compulsory insurance) a major political issue as national defense concerns rose to the fore.[58] Nevertheless, Parran's public health system had already been a key beneficiary of the Social Security Act through the advent of Title VI funds, in which $2 million had been applied to increasing the staff of the Public Health Service itself, and $8 million to the states to improve local services.[59] Through further wrangling in the wake of the National Health Conference, the Public Health Service would be allotted a 50 percent increase in funding by August of 1939.[60] As such, as Allan Brandt has suggested with respect to venereal disease in particular, the expansion of the Public Health Service in general was an important (and relatively unheralded) component of New Deal reform.[61] And Parran's vision of the expanding role for the public health system during this time would be epitomized by his approach to pneumonia control.

At a general level, Parran presented the expansion of the Public Health Service's domain as a contingent outcome of the outpacing of the means for distribution by contemporary medical technology:

> During the past fifty years more progress has been made in the control of disease than in the one thousand years preceding. In our grandfather's time the country doctor riding horseback around the countryside, could carry in his saddlebags most of the medical needs of that day. How different today when medicine stands upon a

> plateau of achievement following the breath-taking ascent of the nineteenth century! . . . The mere acquisition of knowledge in itself means little unless it be translated into action. . . . There is no need for the present wide gap between what we *know* and what we *do* to promote the public health.[62]

Such concerns were crystallized in the attempt to control pneumonia. Speaking before the Missouri Public Health Association on the eve of the National Health Conference, Parran would relate the efforts of a village to cure a patient:

> Just two days ago, I was in a western Pennsylvania town, and the doctor who was to meet me at the train was delayed on a case treating a patient who was ill with pneumonia. He had taken the sputum to the laboratory and found it to be type eight. He telegraphed to Harrisburg and in five hours he had his serum. Serum was given to the patient and he said it was like a miracle the way the temperature came down and the way the patient has improved. But to get that result there was needed a whole working laboratory for typing, and all the various types serving [*sic*] available twenty-four hours a day. There is a need of serum to be made available, but as you know serum is costly, $50.00 to $100 a case. . . . Yet we know that the individual can not pay for this life-giving remedy."[63]

Underlying Parran's approach to such technological and economic contingencies, moreover, was a proposed shift in medical ethics: the replacement of even a utilitarian calculus by the elevation of health care to a *fundamental right* shared by all citizens. Ironically, exactly three months before the invasion of Poland would shift further attention away from such domestic concerns, Parran asserted, in the nation's capital: "Formerly the rich had good medical care as a privilege. During the last generation the poor in some cities have had it as a matter of charity. We now have reached a stage in the evolution of citizenship when all the people, poor and rich alike, are beginning to demand at least a minimum of health protection as a right. . . . To the informed mind, this opportunity for health is beginning to rank with the other basic equalities of American life—freedom of speech, of faith, of assembly, of franchise."[64] For some reformers, compulsory health insurance was required for the protection of such rights; for Parran, the expansion of the public health system—which he would describe as "one of the newest and the most rapidly growing specialties of medicine"—would provide a sufficiently broad safety net held in conjunction with the organized medical profession.[65]

In this respect, Parran faced little active opposition from the medical profession. Remarked a prominent Baylor clinician before the Texas State Medical Association's Section on Public Health in May of 1938:

> I feel that the subject [of antipneumococcal serotherapy] can be discussed with not only a wholesome appreciation of the wonderful clinical achievements in pneumonia therapy, but with an inspired interest in the possible and probable achievements that lie within the province of the public health agencies. . . . Public health in the present and future must be more comprehensive. It is surely the objective of public health endeavor to save human lives, either preventively or curatively. As science and medicine move forward, so must public health, and utilize the various methods provided for saving lives. Such activity cannot be considered an encroachment upon the private practice of medicine. The private physician and health agencies can, and must, establish a cooperative plan for such a program.[66]

And the AMA's Morris Fishbein himself, in a defensive (if atypical) moment at the National Health Conference, remarked: "I am not going to attack government medicine. Since the United States Public Health Service was founded, the physicians of this country as represented by the American Medical Association have given their utmost to cooperate with the United States Public Health Service in every plan for the prevention of disease that has been developed. We are cooperating with Dr. Thomas Parran in his attack on pneumonia, on infantile paralysis, on the venereal diseases. We are willing to cooperate with sound, sane, scientific medical leadership."[67]

Yet Parran would be quick to note that such cooperation remained fundamentally dependent on the dynamics established between the state and its physicians. Six months into his tenure as surgeon general, and less than two years removed from having arranged the "complicated" union concerning pneumonia control between New York state's health department and its medical society, he had explained before the International Medical Assembly of the Inter-State Post-Graduate Medical Association: "Do not mistake me—this wide interest of a health officer does not mean that the health department itself needs to operate or to direct many of the community measures for better health. He should be responsible only for those health services which the individual citizen, the medical profession, the voluntary hospital, and other community agencies are unable to provide. He is concerned, however, that they be provided. This brings up many and complicated problems of relationship between the medical profession and the health department."[68] And the outcome of such joint problem solving was that "the public health may be promoted by using community resources to put better tools in the hands of the practicing physician."[69]

Parran had continued this particular speech by noting that the control of pneumonia itself exemplified the "need for cooperative effort," emblematic of the cod-

dling state-physician relationship required for such achievement. By May of 1940, when Senate subcommittee hearings were conducted regarding "A Bill to Impose Additional Duties upon the United States Public Health Service in Connection with Investigation and Control of Pneumonia, Influenza, and the Common Cold," several public health advocates confirmed his insight. Despite Parran's insistence to Claude Pepper at such hearings that "the medical profession in several States has been more insistent that the health departments do go into pneumonia control than as regards any other public-health activity," the National Institute of Health's representative felt obliged to assert that "the individual physician," rather than the States, was doing the treating, preserving the primacy of the doctor-patient relationship.[70] And while by this time, a nationwide movement to apply Parran's notion of public health expansion to the domain of pneumonia control—initially predicated on the use of serotherapy and eventually extended to the use of sulfa drugs as well—was in full force, the very state-physician dynamics exhibited by the Massachusetts and New York programs had been normalized to form the foundation of the ensuing programs throughout the country.[71]

High-Water Mark: The Pneumonia Control Programs

Despite such resistance to governmental incursion, Heffron, Parran, and their colleagues had achieved their objective: to transform pneumonia not only into an individual emergency but into a national public health emergency as well. This transformation occurred through the nationwide growth of state-controlled, yet federally financed, pneumonia control programs. Indeed, while the rise in post–New Deal funding for the treatment of such classic public health concerns as venereal disease and tuberculosis has been well documented,[72] for a brief period beginning in the late 1930s, with Parran's imprimatur, pneumonia was recast as nearly as pressing a national public health menace as such traditional counterparts.[73]

In late 1936, Met Life's Donald Armstrong had again played catalyst, intimating to Parran that "the time is ripe for some agency to do a thoroughgoing informational and promotional job [with respect to pneumonia], with state health departments, state medical societies, and eventually with the public."[74] Parran, fresh from having initiated the New York program, needed little urging to envision such a "campaign";[75] and despite the reservations of the American Medical Association's leaders about becoming involved, a national Advisory Committee on Prevention of Pneumonia Mortality (whose members included Armstrong, Cecil, and Heffron, among other pneumonia control veterans) was convened by

November of 1937, with an intention "to obviate further delay in the development of sound and comprehensive programs designed to reduce pneumonia mortality."[76]

During the discussion on the "expansion of general public health services" at the National Health Conference itself in July of 1938, pneumonia was discussed immediately following tuberculosis and venereal disease, and prior to cancer, malaria, mental hygiene, and industrial hygiene, respectively.[77] An annual appropriation of $22 million was recommended for pneumonia control, with half of such funding to pay for serum.[78] And while, in the setting of the failure of the National Health Program, the actual federal funding of the state pneumonia control programs would hardly approach such magnitude (nor, for that matter, would that of tuberculosis or venereal disease control), their funding would nevertheless climb nearly sixty-fold between 1937 and 1940.[79] Indeed, by 1940, with such federal support, approximately two-thirds of the nation's states and territories would boast pneumonia control programs.[80] The development in some states was dramatic.[81] For example, in Illinois, the Title VI federal largesse in general appeared after 1936 "almost like manna from heaven and in amounts only dreamed of a year or so previously," leading to an expansion of Illinois' entire state public health infrastructure.[82] Regarding pneumonia control, the state's public health department had complained in 1934 that "there continues to be very little interest in pneumococcus typing in Illinois, probably because a great deal of serum treatment of pneumonia is not being used." However, by 1939, 120 typing stations and 12 serum centers had been created and were responsible for the typing of 2,071 sputum samples and the provision of serum for 1,016 cases of pneumonia (at a combined serum expense of $54,254 for the first six months of that year alone).[83]

The rapidity of such expansion—in which, as Harry Dowling has noted, some states simply plunged into pneumonia control for the sake of acquiring funding—was cause for concern among such a serotherapy advocate as Cole, who feared the dilution of the intensive treatment of pneumonia in such a context.[84] But for most of the pneumonia vanguard, these were welcome problems, to be solved with the continued transformation of physician attitudes.[85] And what would necessarily have to parallel such physician education would be that of the laity as well. Dowling has retrospectively downplayed the role of such lay publicity, focusing on the hesitation of state public health departments to inform patients prior to the re-education of physicians.[86] This characterization may apply to some degree to the pre-1938 era,[87] but given the contemporary consideration

that "the public must have knowledge of the cardinal symptoms of pneumonia in order that the family physician may be summoned on the development of the first symptom of the disease," by 1938 such lay publicity itself was deemed essential.[88]

The primary source of such publicity emerged from the national efforts of the U.S. Public Health Service, often in conjunction with the Metropolitan Life Insurance Company.[89] Their most visible "joint" production was the twelve-minute film *A New Day,* sent to theatres with recommended "exploitation hints" and attached media, from stills to prefabricated newspaper editorials.[90] Pneumonia—as a specific emergency mandating that the public, their physicians, and the public health apparatus unite to provide in timely fashion the wonders of the modern specific—had thus been reformulated in literally dramatic fashion before the nation at large (see Figs. 1–4).

Strong state programs (as has already been shown with respect to New York, where no hesitation concerning lay publicity had been apparent) were likewise quick to use various media, from written pamphlets to radio and live presentations, as means of public education. In Pennsylvania alone, between January and October of 1940, 122 meetings were conducted before a total of 44,289 people.[91] Such state publicity efforts, however, were highly variable, reflecting the variability in size and scope of the pneumonia control programs themselves. Indeed, "control" itself ranged from the provision of specifics to the indigent and the central monitoring of consequent therapeutic efficacy, to the mere ensuring that statewide laboratories were capable of around-the-clock pneumococcal typing.[92] Certain of the largest programs—such as those of Massachusetts, New York, Pennsylvania, Minnesota, and New Jersey—arose from traditional public health strongholds.[93] Yet while the formation of the programs did often reflect such traditional public health emphases, a large degree of local prioritization by reigning state health department personnel was apparent as well: the rural states of North Dakota and Iowa, for instance, boasted impressive programs relative to the number of citizens covered (and especially considering the population density of such citizens), while such traditionally public-health-oriented states as Indiana and California appear to have boasted none.[94]

A key variation among the participating states, finally, concerned the nature of the specifics they provided. The pneumonia control programs had been predicated on the laboratory-intensive nature and high cost of antipneumococcal serotherapy. But by early 1939 sulfapyridine—the first effective antipneumococcal sulfa drug—had been introduced nationwide, representative of the emerging

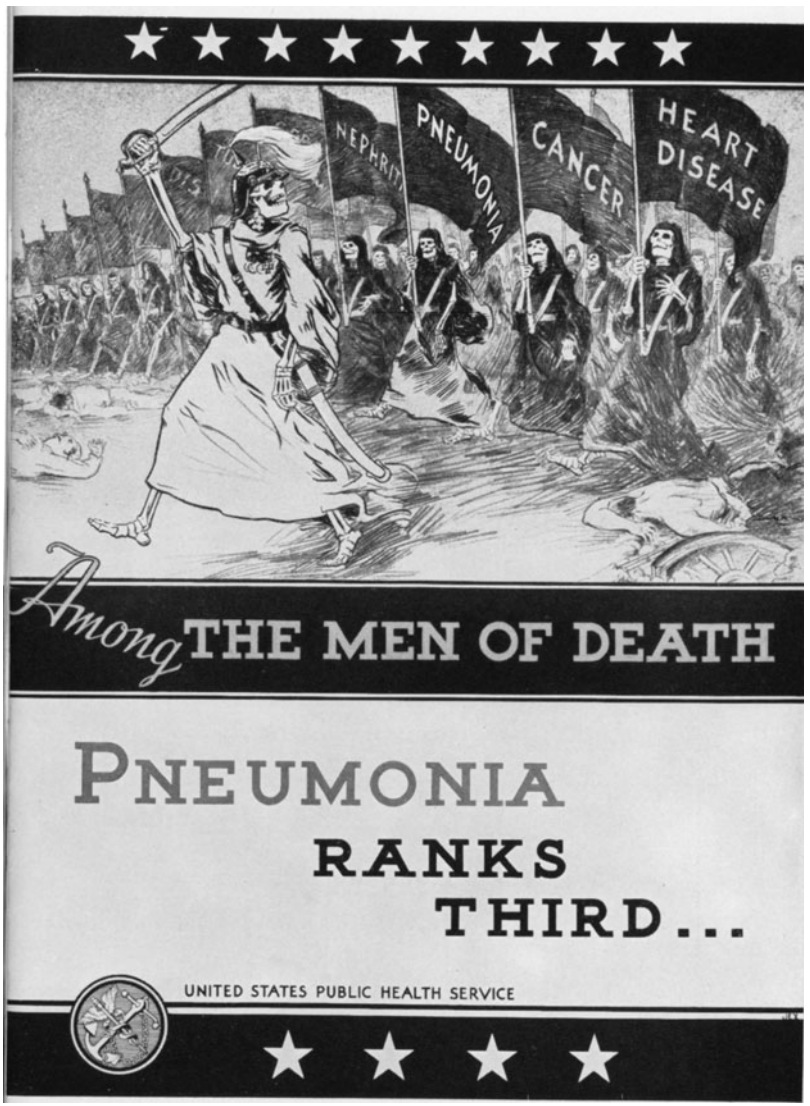

Figure 1. Despite the ascent of such chronic diseases as heart disease and cancer to the top of the nation's leading causes of death by the late 1930s, clinicians were reminded that pneumonia remained the leading infectious cause of death in the nation. The disease's prominence was thrust before practitioners alongside the apparent means of reducing such prominence. [From *Pneumonia: Some Important Facts Regarding Treatment and Control* (Washington, D.C.: U.S. Government Printing Office, 1940), 7.]

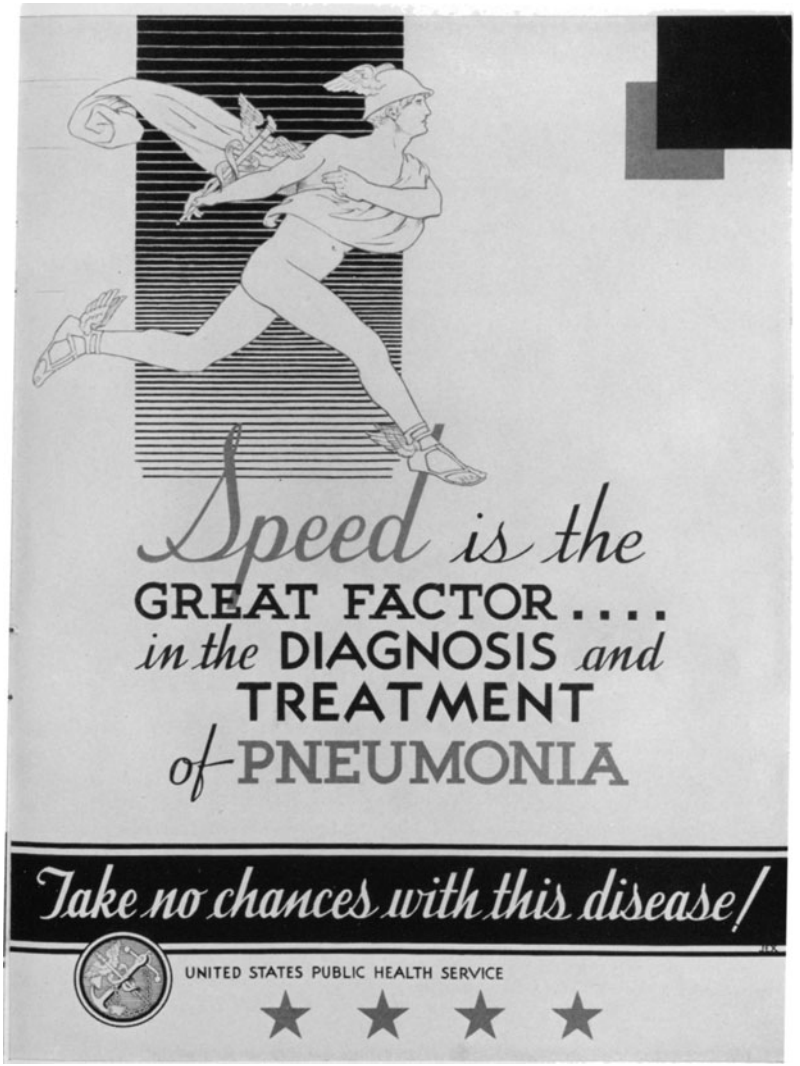

Figure 2. Given what was known of the importance of the "door to needle time" (to use an anachronism) of antipneumococcal serotherapy, pneumonia was explicitly reformulated as an "emergency" in the 1930s, as pressing as appendicitis, to which it was often compared. Such a reformulation also helped to justify the need for pneumonia control efforts, in hopes of providing clinicians with serum as soon in the course of a pneumonia case as possible. [From *Pneumonia: Some Important Facts Regarding Treatment and Control* (Washington, D.C.: U.S. Government Printing Office, 1940), 21.]

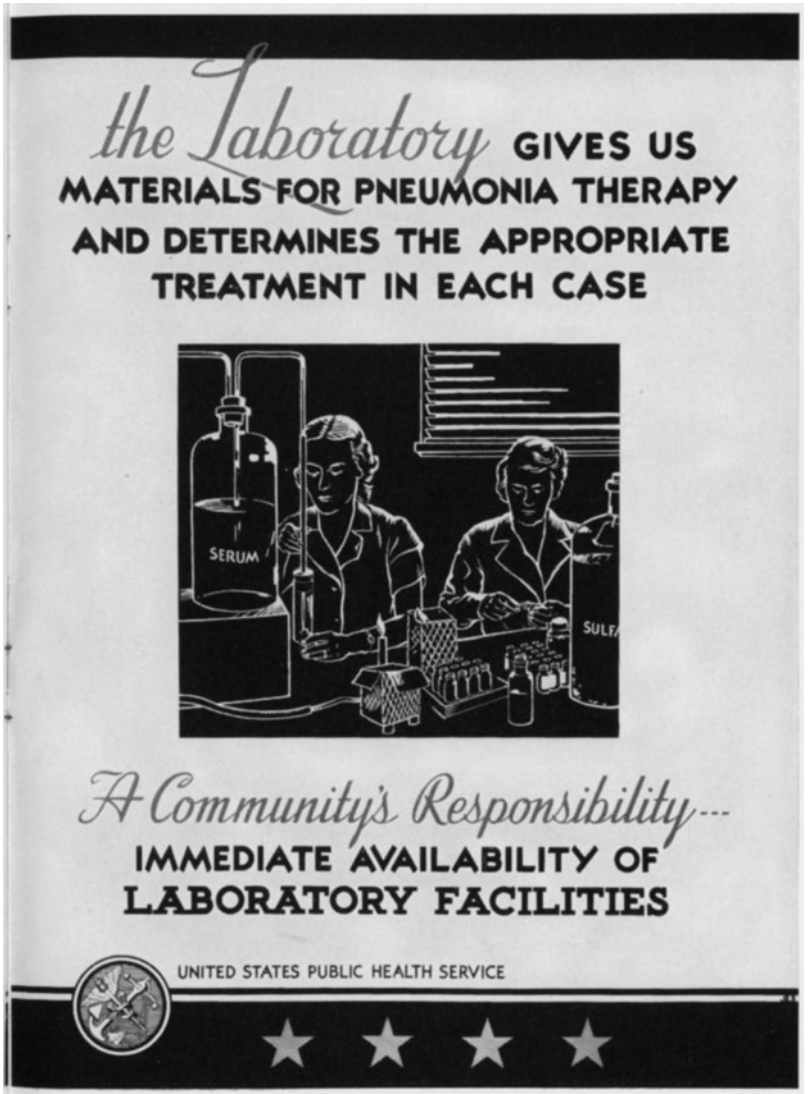

Figure 3. Given the logistics of serotherapy, the treatment of the individual patient was transformed into a "community's responsibility." By 1940, however, the sulfa drugs were already in the midst of displacing serotherapy, and would soon contribute to pneumonia's dissolution as a public health concern. [From *Pneumonia: Some Important Facts Regarding Treatment and Control* (Washington, D.C.: U.S. Government Printing Office, 1940), 27.]

Figure 4. In an era of intense resistance to the encroachment upon the domain of the private practitioner by the American Medical Association, the United States Public Health Service attempted to portray its role as one of friendly guide, rather than usurper of individual practice. With the advent of the sulfa drugs, however, such "advice" would be considered no longer necessary. [From *Pneumonia: Some Important Facts Regarding Treatment and Control* (Washington, D.C.: U.S. Government Printing Office, 1940), 29.]

chemotherapeutic "revolution" as applied to pneumonia. State responses varied. At one end of the spectrum, such a longstanding serum supplier as the Massachusetts Department of Public Health continued to offer serum alone to its populace, leaving patients to purchase for themselves the less expensive sulfa drugs.[95] New York's State Department of Health—which continued to provide free serum and which would refrain from sulfapyridine distribution until 1941—provided its own warning in its 1939 report:

> While it is felt that the full potentiality of [sulfapyridine] in the saving of lives has not yet been realized, it is also felt that the medical profession has not had sufficient opportunity to define the limitations of this drug nor to acquaint itself thoroughly with the relative place and merit of the two powerful specific agents, serum and sulfapyridine, now at its disposal. . . . The continued progress in the production and effectiveness of specific antiserums, coupled with a growing conviction that this approach is so fundamentally sound that it must be further developed, results in a responsibility toward these biological therapeutic agents which momentarily may be lost sight of in the brilliance of advances in the field of chemical therapeutic agents.[96]

In contrast, the administrators of Tennessee's pneumonia control program—who decided after the program's inception in 1940 to provide only sulfapyridine to practitioners—countered a year later: "As compared with the serum therapy, chemotherapy has a greater range of usefulness, is very much less expensive, is much more easily administered, is generally more readily available, is more potent and is no more likely to be attended with specific, seriously harmful effects."[97] A diversity of intermediate approaches could be found across the country, depending on the inception dates of the programs, their previous investments in serotherapy and typing stations, and the inclinations of their leaders.

As Tennessee's own public health department would note, however, the affordability of the sulfa drugs would eventually erode the very basis for the existence of the pneumonia control programs, contributing to their demise by the end of World War II.[98] Such a process would again alter—irrevocably, to this point—pneumonia's tenuous status as a public health issue, as will be delineated in chapter 8. Yet the transformation from the serotherapeutic to the chemotherapeutic and antibiotic treatments of pneumonia offers more than just an explanation of the decline of the pneumonia control programs. Conversely, and equally striking, antipneumococcal serotherapy's preeminence by the 1938–39 pneumonia season—especially as fostered by the pneumonia control programs—would have a

tremendous impact on the sulfonamide "revolution" itself as applied to pneumonia. Part III will delineate this revolution in detail, examining more finely the substance of this notion as applied to modern therapeutic change in general as well as exploring the consequences of its rhetoric for the American medical profession's approach to respiratory infections in particular.

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Histology of a Revolution

Histology, of course, depends as much on the mode of presentation of materials as it does on a magnified viewing of its subject. For ease of presentation, I have therefore divided this longest chapter into three chronologically ordered subgroupings, highlighting: the resistance engendered by serum advocates against the abandonment of antipneumococcal serotherapy during the advent of the sulfa drugs; the resultant (if heterogeneous) persistence of antipneumococcal serotherapy to a degree hardly captured by images of wanton rabbit warren and horse farm destruction; and finally, the course of antipneumococcal serotherapy's ultimate displacement. I hope, in the process, to have made visible the necessary complexity of such a therapeutic transformation while providing a substrate from which to draw more universal principles.

Resistance: Therapeutic Control

As demonstrated in the previous chapter, by the late 1930s serum was becoming increasingly advocated as the standard of care of the pneumonia patient, embedded in a public health approach to pneumonia and unanimously supported in the medical literature. In October of 1938, a Pennsylvania practitioner encouraged the fellow members of his own decidedly pneumonia-conscious state medical society to advocate for further state funding for serum, "which will surely be needed in larger amounts as specific treatment becomes more popular."[1] The same day, in Indiana, a clinician would note before the Indiana State Medical Society: "It has been stated, and it must be repeated, that pneumonia is one of the great medical emergencies. It demands aggressive attention, just as does the acute appendix, perforated ulcer, diphtheria or coronary occlusion. . . . It is evident that specific type serum therapy of pneumonia is established, and it should be pressed until some better method is developed."[2] As further substantiation of such support, in several prominent trials of the sulfa drugs for pneumonia, only

those patients with pneumonia considered less amenable to serotherapy were subjected to the "experimentation" of treatment with the sulfa drugs in the first place.[3] Indeed, some still conceived of antipneumococcal serotherapy as a paradigm for the serotherapeutic approach to *all* infectious diseases.[4]

Sulfa advocates were certainly present and propagating, however. In 1935 Germany's Gerhard Domagk had announced the treatment of murine hemolytic streptococcal infection with the azo dye later named Prontosil; and after initial skepticism, researchers in Great Britain and the United States found that a derivative of Prontosil, sulfanilamide, indeed appeared effective in such streptococcal infections as puerperal fever and erysipelas.[5] Through pharmaceutical company and media promotion, sulfanilamide would, over the next several years, indeed initiate the chemotherapeutic revolution.[6] As applied to pneumonia in America, proponents from several academic centers (most prominently, the Detroit Receiving Hospital) lent their weight behind the novel agent in the treatment of pneumonia, whether nonspecifically against all pneumococcal serotypes, or either alone or (in anticipation of future trends) in *combination* with serotherapy against the ominous type III pneumococcus.[7] And certainly, clusters of general practitioners did use the novel agent for such a relative of the beta-hemolytic streptococcus as the pneumococcus.[8]

In general, however, the marginal benefits accorded to sulfanilamide were considered to be outweighed by its novel *toxicities* (from headaches to life-threatening hemolytic anemias and cyanosis) at pneumonia-level doses, as the sulfa drugs faced the same stigma regarding novel side effects that had plagued the now-familiar serotherapy years earlier. An exchange between Harvard's Max Finland (an advocate of combination therapy for type III pneumococcal pneumonia) and Wesley Spink (at the University of Minnesota) in late 1937 suggests the contemporary weight given to the novel sulfanilamide's side effects and efficacy, vis-à-vis those of serotherapy, by two leading specialists:

> [Finland to Spink:] [Regarding sulfanilamide,] we have encountered the whole gamut of untoward reactions. In some instances they were so severe and death was experienced so that the workers were very hesitant to use the drug. [Isadore] Snapper in Amsterdam made the blatant remark that the wave of enthusiasm for this drug has long been passed here in Europe [where Finland was visiting].[9]

> [Spink to Finland:] You may be interested to know that we have had on the service recently a mother and her 17-year-old son, both with type 2 lobar pneumonia. The son had also otitis media of the right ear, type 2 pneumococci being recovered and the mother had a type 2 bacteremia. Both recovered with serum therapy. We also re-

> cently had a young woman on the service with a type 4 lobar pneumonia with bacteremia. Her pour plate was just peppered with colonies. We gave her sulfanilamide in large amounts, titrating the blood at the same time, but she died. . . . P.S. What is the present status of sulfanilamide therapy in pneumococcal infections?[10]

Shaky, at best, was the answer. At the same time, Jesse Bullowa wrote to Met Life's Louis Dublin: "The value of sulfanilamide in Pn.III is by no means established, and it should be emphasized that these dyes are like a sword with two edges and may interfere not only with the germ, but also with the life of the patient."[11] Even Alvin E. Price, the head of clinical studies at the Detroit Receiving Hospital, remained too wary of sulfanilamide's apparent tendency toward the induction of hemolytic anemia at "massive" pneumonia-level doses to recommend its general usage outside the strict monitoring of the hospital.[12] Moreover, such sentiments were echoed the very same week at the Southern Medical Association, where the use of sulfanilamide for pneumonia was deemed to be nearly as appropriately confined to experienced specialists as the use of artificial pneumothorax (insertion of air into the pleural space).[13] The specter of sulfa toxicity, on top of serum's proven efficacy, precluded any simple revolution.

Such emphasis on side effects would likewise initially dominate the introduction of the efficacious—and eventually triumphant—sulfapyridine in the winter of 1938–39. In May of 1938 the University of London's Lionel Whitby had announced the apparently successful treatment of murine pneumococcal infections with the sulfanilamide derivative sulfapyridine (termed M&B 693, given its synthesis at the British pharmaceutical firm, May and Baker).[14] Within two months, two of Whitby's countrymen had reported in the *Lancet* their alternate control trial demonstrating the efficacy of sulfapyridine for the treatment of pneumococcal infections in humans.[15] But prominent physicians in the United States were wary from the outset regarding sulfapyridine's potential toxicity (which seemed, among other things, less controllable secondary to the drug's unreliable absorption).[16] Harry Marks, moreover, has cogently related the manner by which Congress—outraged by the deaths in 1937 of over one hundred patients at the hands of sulfanilamide dissolved in diethylene glycol—enacted the Federal Food, Drug, and Cosmetic Act of 1938, allowing the FDA to use sulfapyridine as a first test case by which to ensure the safety of a medical remedy *prior* to its interstate sale and distribution to general practitioners.[17] On account of the Act, Merck, applying in October of 1938 to distribute sulfapyridine in the United States, was indeed forced, throughout the winter of 1938–39, to test the remedy in an extensive number of monitored hospital settings to ensure its safety prior to such authorization.

The FDA, in the last months of 1938, focused on sulfapyridine's toxicity in absolute terms. The drug's most obvious adverse effect was the inducement of marked nausea and vomiting. An actual supporter at Presbyterian Hospital in New York deemed it the best emetic he had ever come across,[18] while Max Finland would later in the season bring his and Wesley Spink's discussion forward from the sulfanilamide to the sulfapyridine era with striking parallels: "We have been having considerable difficulty in getting our intern staff to administer this drug. Most of our interns would prefer to stay up all night giving serum therapy, knowing that their patients will be well the next morning, rather than face their depressed, cyanotic, vomiting and extremely ill patients during the ensuing days."[19] These observable phenomena, moreover, were compounded by emerging fears and findings concerning sulfapyridine's potential to cause such life-threatening complications as renal toxicity, hemolytic anemia, and hepatitis.[20]

Nevertheless, the FDA's evaluators were increasingly impressed by sulfapyridine's clinical efficacy, becoming sulfapyridine advocates by December; and as Marks has indicated, by this time they had moved from a conception of sulfapyridine's toxicity in absolute terms to a utilitarian calculus that considered its relative toxicity with respect to its efficacy.[21] Yet such advocacy represented one side of a schism in contemporary opinion regarding the general release of sulfapyridine that would emerge at several levels. By December, in contrast to the pro-sulfapyridine leanings of the FDA investigators, both state and federal public health administrators—many of them integral to the diffusion of antipneumococcal serotherapy—offered heated resistance. As New York's Commissioner of Health, Edward S. Godfrey, implored his predecessor, Surgeon General Thomas Parran:

> The simplicity of the administration of the drug would very possibly lead to the replacement of serum therapy if released for general distribution. Since there is not satisfactory evidence of the effectiveness of this compound in any single type of pneumonia, and since there is increasing evidence of reactions produced by it which are similar and possibly more severe than those produced by sulfanilamide, release for general distribution would seem to be, in the light of present knowledge, an extremely dangerous procedure. . . . May I suggest that you use your influence in preventing the release of this drug for general distribution until such time as sufficient data may be carefully collected and analyzed in order that the efficacy of this drug in the various common types of pneumonia may be determined and its toxicity adequately measured.[22]

Parran—whose top advisors concurred in such an opinion—was happy to oblige, relaying to the FDA's chief the concerns of the New York State and New York City

Pneumonia Advisory Committees, "with the statement that they are in complete agreement with the opinion of the Public Health Service upon this subject."[23] And such a standpoint represented one instance in which Parran was supported by the AMA itself, through the cautious recommendations of its own Council on Pharmacy and Chemistry.[24]

Faced with this division in opinion, by January of 1939, the FDA stalled on releasing the sulfa drug and expanded its own investigation by querying dozens of leading clinicians and researchers regarding the advisability of sulfapyridine's general release.[25] A majority of those queried were in support.[26] Moreover, on January 18, 1939, when approximately five hundred clinicians clamored to attend a New York Academy of Medicine symposium on the potential wonder drug, the proceedings were switched from a smaller meeting room to a large auditorium. The accounts of the symposium were "quite glowing, and optimistic, and the emphasis was definitely on the favorable side."[27] The University of Pennsylvania's Harrison Flippin, leading the largest (if uncontrolled) study of sulfapyridine, concluded the meeting by publicly stating that "the use of sulfapyridine met with considerable opposition when its use was first begun in Philadelphia but this opposition is disappearing," adding "facetiously" that "a few of the old style physicians still use serum."[28]

Bellevue's William Tillett continued such a deprecation of serotherapy in the wake of the meeting (as well as in the wake of persisting uncertainty regarding the degree of serotherapy's dissemination), as reported by the FDA's representative:

> In discussing the possible danger which might result from physicians' discontinuing serum therapy if [sulfapyridine] were made available to them, and thus causing an increase in pneumonia mortality rather than a decrease in case the expectations from this drug were unfounded, or the toxic effects too great, . . . he stated it was his experience that serum is not used so extensively as some would have us believe; that the facilities for using it properly are confined to a very small group of physicians, and that, in his opinion, this criticism was not a valid one.[29]

One could argue that the emerging public health apparatus countered such a claim, but other clinicians attacked the public health system's entrenched advocacy of serotherapy itself. As Roosevelt Hospital's medical director reported: "The Pneumonia Control Board at Albany . . . is a serum-typing agency and serum treatment agency. . . . The statement that there is no evidence that this drug is of value in pneumonia is fantastic and apart from the facts; . . . they just did not want to abandon a long-settled plan of work."[30] Still others sought to strike preemp-

tively at such serotherapy supporters as Bullowa, as when one clinician stated to the FDA's investigators: "This drug is going to put Dr. Bullowa and his serum out of business, and you should take any criticism Dr. Bullowa offers with several grains of salt, because he is in the serum business."[31]

Yet even such wary sulfapyridine supporters underestimated the extent of advocacy for serotherapy that Bullowa and his colleagues at the pneumonia vanguard would continue to provide at the same time, offering a replication of the FDA–Public Health Service dichotomy. Bullowa began in conciliatory fashion at the New York Academy of Medicine, hoping to maintain serotherapy's position alongside, if not to the exclusion of, sulfapyridine. Advising the audience "not to throw overboard all knowledge and weapons accumulated in the last 20 years," he retreated somewhat, admitting that "it is safe to omit antibodies at first," but then sternly injected that "if there is no response in 18 to 20 hours, the physician is toying with the life of the patient and it may be well to add antibody."[32]

From such a tenuous position at the meeting, serotherapy's supporters advanced still further on the offensive, attacking sulfapyridine's putative efficacy, stressing its apparent toxicity, and most importantly, warning of its potential to lead to the dissolution of the tried and true specific, antipneumococcal antiserum. Lloyd Felton (as he had with sulfanilamide two years prior) impeached the efficacy of sulfapyridine in the treatment of experimental murine pneumococcal infections,[33] while Hobart Reimann, at Jefferson, attacked the uncontrolled nature of the crosstown clinical sulfapyridine studies at Penn.[34] Finally, David Rutstein (then serving on the New York State Health Department's Bureau of Pneumonia Control) criticized the very lack of concern with pneumococcal specificity that sulfapyridine had embedded in such clinical studies, pointing out that there was "not as yet significant evidence of the efficacy of this drug in any single type of pneumonia."[35]

Focusing on sulfapyridine's toxicity in absolute terms, Finland expressed his fear that given the drug's simplicity of administration, not only might it be generally utilized prior to the full discovery of such effects, but that it was "not unlikely that *many* persons will receive the drug for each person in whom the drug is even remotely indicated," potentially compounding the population burden of sulfapyridine toxicity.[36] But in constructing their own therapeutic calculi, those wary of the general release of sulfapyridine appeared to fear most the expected decline in the use of serotherapy incumbent upon such release. As the University of Chicago's Oswald Hope Robertson related to the FDA's chief:

> Immediate distribution of this drug, which I regard as inadequately tested, to the profession at large would undoubtedly discourage the use of antipneumococcus im-

> mune serum, which is rapidly becoming a widely used procedure and one which has been shown to be highly effective in lowering the death rates of almost all types of pneumococcus pneumonia. While sulfapyridine may be an effective therapeutic agent in this disease, we certainly have no evidence as yet that it is nearly as effective as antipneumococcus serum, so that the substitution of this chemotherapeutic agent for immune serum might as well result in much more harm than good.[37]

Likewise, Bullowa, emboldened from his position at the Academy of Medicine, stated to the FDA his expectation "that the definite restriction should be placed on the label that . . . [sulfapyridine] is not to be substituted for serum therapy."[38] The AMA's Council on Pharmacy and Chemistry continued to oppose sulfapyridine's general release, publishing in the *Journal of the American Medical Association* in February:

> In the light of evidence now available, the general use of sulfapyridine does not seem to be warranted at the present. Because of its definitely experimental status, the drug should be used under conditions of controlled investigation. Under the new law passed by Congress in 1938 a new drug may not be released for interstate sale until it has been licensed. Under the regulations, manufacturers of new products may obtain permission for properly qualified workers to investigate the preparations. The Food and Drug Administration has a great responsibility. It has not released sulfapyridine for general sale in interstate commerce and for this action it deserves commendation. The law gives opportunity for the first time for a drug to be tried *first* in hospitals which have facilities for observing all its manifestations. Such a procedure is established in the interest of the public and is much preferable to the former custom of frequently placing the drug on the market before adequate tests had been made.[39]

Bullowa, Norman Plummer, and Finland publicly stated their case in the same issue, as they warned in a letter:

> In the case of only one group of agents, namely type-specific antipneumococcus serums for the treatment of pneumonia due to certain types of pneumococci, have the experimental and clinical results been consistently favorable. During recent years these serums have received increasingly widespread acceptance coincident with improvements in the quality and potency of the serums produced and particularly with the recent introduction of antipneumococcus rabbit serums and improved efficacy of typing. As far as can be ascertained, all who have had the opportunity and have been willing to use good specific serums under well controlled conditions have been uniformly impressed with the striking clinical responses and

> with the marked reduction in mortality in the pneumonias due to the types of pneumococci for which specific serums have become available. . . . A number of . . . workers are now engaged in an earnest effort to evaluate [sulfapyridine], with its benefits, limitations and dangers. They are attempting to learn the proper methods of using the drug in order to obtain the optimum of benefit with the minimum of harm. While such investigations are in progress and until the results of these studies are carefully analyzed and assessed, it is well to retain and to use the proved remedies. It would be unfortunate if the appearance of a new therapy, no matter how promising, were to cause the abandonment of agents whose curative efficacy and life-saving qualities have become established. In the case of pneumonia, sulfapyridine must still be considered as an experimental drug and, as such, should be used only under controlled conditions."[40]

"Control," in the clinical epidemiological sense (as will be discussed in chapter 7), would soon mean very different things to each of the three authors; but for all three "therapeutic rationalists," the control of the therapeutic encounter itself seemed most at stake at this time.[41]

Nevertheless, as each week passed, the emerging clinical data placed sulfapyridine in an increasingly favorable light.[42] By the end of February, the U.S. Public Health Service's representatives—once their attention was again focused on the merits of sulfapyridine alone—agreed to its general release, leaving the problem of the relative utility of serum and sulfa to clinicians and time to sort out.[43] Bullowa himself assented to such reasoning the very same week;[44] and on March 9, 1939, sulfapyridine was finally released for interstate sale.

But the resistance offered against its general release had certainly stemmed an immediate revolution. The first published accounts by Flippin's group on sulfapyridine's utility were heavily weighted with concerns regarding its toxicity, as exemplified by the tepid conclusion: "If sulfapyridine is used with regard for its toxic possibilities, and if the patients in whom it is used are thoroughly studied and carefully followed, it is a therapeutic agent with a satisfactory margin of safety."[45] And the FDA's own investigators, in their final evaluation prior to releasing the drug, expected a protracted negotiation between the use of sulfa and serum among clinicians. As they summarized the collective opinion of those clinicians who favored sulfapyridine's release: "Whether or not this drug will supplant serum will require years to determine. Many people will be saved by this drug who do not have access to serum, have more than one type of pneumococcus in their sputum, or have a pneumococcus which does not definitely type. This drug need not supplant serum; it can be used as an adjunct, and with serum un-

til this question has been definitely answered."[46] It seems that serum's supporters had indeed forestalled the immediate destruction of the rabbit hutches.

Persistence: Therapeutic Heterogeneity

There remained good reason, however, for the enthusiasm and impatience evident in such lay venues as *Colliers* and the *New York Times*.[47] In elaborating on the formal calculus in his William Beaumont Lecture, delivered the same month his co-authored letter appeared in *JAMA,* even as staunch a serum supporter as Bullowa had to dyspeptically admit the sulfa drugs' chief advantages: their ease of administration, their "alleged" nonspecificity with respect to pneumococcal types, and most importantly, their reduced cost.[48] Plummer and Herbert Ensworth, too, by May of 1939, proclaimed such advantages still more stridently at the AMA meeting's section on pharmacology and therapeutics.[49] Of course—and despite the claims by some that the sulfa drugs could potentially be *less* toxic than their serum counterparts[50]—sulfapyridine's seeming ease of administration and nonspecificity, when vulgarized by local practitioners through careless empiric administration, could represent the clinical Cassandras' worst fears realized. Remarked two transgressing sulfa advocates from Maine:

> The simplicity of this drug treatment is a great advantage. Immunotherapy requires frequent intravenous administrations of the serum and consequently the physician must be in almost constant attendance over a period of twelve hours or more while the treatment is carried out. This drug, however, is given orally and does not require such close supervision. . . . The necessity of typing sputum is eliminated. Although it might be of academic importance to know whether it is a pneumococcal pneumonia that one is dealing with, response to the use of this drug would give one an indication of the infecting organism.[51]

Nevertheless, it would be difficult to argue against the newer economic deal afforded by the sulfa drugs. While serotherapy's supporters continued to justify its expense in terms of concomitant reductions in length and cost of hospitalization (or by the tired comparison to funeral costs),[52] sulfapyridine, initially reported to cost less than one-fourth that of serum on a case-by-case basis, would soon be determined via direct comparison to be more than twenty times cheaper ($3.03, compared with $70.07, per patient).[53] Such differences held manifest practical consequences. As two Nebraska State Hospital investigators, echoing such findings, would confess: "We have not been particularly concerned with the physiological or pharmacological action of this chemotherapeutic agent. What we

were essentially interested in was an economic evaluation since the cost of adequately and successfully treating physical and mental illnesses becomes a very trenchant and pertinent actuality in a hospital of this type."[54]

As winter turned to spring in early 1939—and in the context of the competing advantages and disadvantages between serotherapy and sulfapyridine for the treatment of pneumococcal pneumonia—an impressive variability appears to have characterized the usage of one agent versus the other across the country. A survey of approximately one hundred sulfapyridine investigators published in May by the AMA's Council on Pharmacy and Chemistry already hinted at such prevalent heterogeneity: "Some clinics have found that many cases of pneumonia are particularly susceptible to the combined use of specific antiserum and sulfapyridine. Certain investigators enthusiastically prefer sulfapyridine to antiserum in the treatment of pneumonia in adults. Others advocate it more particularly in pneumonias for which there is no available antiserum."[55] One of sulfapyridine's leading advocates would retrospectively polarize such variability along the lines of entrenched urban serum advocates versus rural general practitioners eager to avail themselves of the seemingly simpler sulfa agents.[56] Yet while this characterization of such urban advocates as Bullowa and Finland (who cautioned against comparing sulfa results against historical serum outcomes, given the equally rapid, ongoing and startling advances made in serotherapy) is borne out,[57] the generalization of the profession along such boundaries misses the extraordinary roles—enhanced by the critical influence of the pneumonia control programs—that personal preferences and local contingencies and chains of reference would play in generating variation in serum versus sulfa usage across the country, within states, and even among and within particular hospitals at this time.

From Nebraska, for instance, from whence the aforementioned "economic" call for sulfapyridine had originated, would come equally forceful warnings not to abandon an established specific for an unknown—if enticing—upstart: "We should sell the Profession and the public the value of the serum. This includes selling it in our town and in our state. Sulph-pyridin [*sic*] may be its rival in halting the march of death but until we know more about it we should sell the known."[58] And also: "There is a too inherent natural tendency for us to consider the most recent discovery as automatically the best, and to neglect known dependable methods. It would be much wiser for us to follow the advice of the writer who said, 'Be not the first by whom the new is tried, or yet the last to cast the old aside.'"[59] Rebutting the easy dichotomization of serum versus sulfa along hospital versus home treatment lines, moreover, some of the most ardent supporters

of the treatment of pneumonia in the home at this time were equally fervent in their support for serotherapy:

> Let us see how we can keep the pneumonia patient at home and yet treat him as well as if he were in the best equipped hospital in the land. By providing ourselves with a few vials of typing serum and a microscope, we can easily type the organism and determine whether a potent anti-serum is available. Neufeld's capsule-swelling reaction is so definite when positive that it hits one in the eye so to speak. . . . In case your pneumonias do not type out, sulfanilamide, or its new form, sulfapyridine, may be found very helpful, but I for one can not put my faith in these drugs alone when we have a specific of proven value when these have not stood the test of time as yet.[60]

Of course, by early 1939 such home and local hospital treatment had more typically become linked with the efforts of the pneumonia control programs. Recalled one rural Minnesota practitioner, proudly relating the advances in rural communication and transportation through which the Minnesota State Board of Health could provide him with rapid typing services and serum (even if only, in his case, to combine with sulfapyridine in the treatment of pneumonia): "The administration of anti-pneumococcic serum according to type is the logical treatment. . . . Pneumonia cases can be typed with speed, and treated with efficiency in rural communities, by country doctors and in spite of and without the benediction of Hugh Cabot, who has belittled the value of 'country doctors.'"[61] In still more avid fashion, during the U.S. Senate hearings on the "Investigation and Control of Pneumonia, Influenza, and the Common Cold" in May of 1940, the director of the Illinois State Department of Health's enthusiastic Division of Pneumonia Control presented a fistful of letters received from physicians during the previous year. Emblematic was a letter written almost exactly one year before the Senate hearings:

> I am enclosing my report on a case of serum-treated pneumonia and can't help but be a little more enthusiastic than a routine report. This patient, a 13-year-old lad . . . was seized with a chill and pain in the left chest . . . and I was called 24 hours later and found a full-blown textbook picture of lobar pneumonia. . . . 1 hour prior to the institution of serum therapy the boy's temperature was 106 axillary, his pulse 160 and very irregular, respiration were [*sic*] 44 and very labored and the boy was absolutely cyanotic. Since this was the first case of serum treatment in our hospital, I invited the staff to see him and about 10 of my colleagues agreed that serum was his only hope. . . . [The following day] the patient was rational and said he was comfortable which was a contrast to the delirium of the day before. On the following morning his temperature was normal and he has made an uneventful recovery. I

> firmly believe that this is one case literally pulled out of the fire and wish to take opportunity to thank you and your department for the splendid pneumonia program. In conclusion I might add that we had sulfapyridine ready and was [*sic*] tempted to use it but felt the serum should be given a free rein. The plan was to start the drug the second day if no improvement was noticed. Needless to say it was not used.[62]

Such Midwestern enthusiasm, moreover, was bolstered by May of 1939 by a homegrown (and fairly extensive, if self-admittedly methodologically flawed) report before the AMA meeting in St. Louis, demonstrating the apparent superiority of serotherapy over sulfapyridine.[63]

But by the end of spring, the first (though likewise non-alternated) pro-sulfa comparison study emerged—at the very least, publicly declawing the bugbear of sulfapyridine's purported fatal side effects.[64] Given sulfapyridine's low cost, enthusiasm spread quickly in many areas. Noting the hyper-enthusiasm apparent to him, Robert A. Kilduffe, director of the laboratories of the Atlantic City Hospital, sounded the (admittedly positivistic) warning at the Annual Meeting of the Medical Society of New Jersey held in *his* backyard in June, that drugs must pass through waves of such hyper-enthusiasm and hyper-pessimism before arriving at a rational third stage "when time and cumulative results of continued study enable logical and unbiased evaluation."[65] As such, he echoed the Council on Pharmacy and Chemistry's own cautious assessment of the previous winter's encouraging studies of sulfapyridine: "The reports deal only with the treatment of one year's series of pneumonia cases. The relative virulence of pneumonia during this particular period cannot be established beyond any question of doubt and therefore it is essential to employ this chemical agent over a period of years before the extent of its usefulness both alone and as compared with specific antiserum can be definitely determined."[66] Conflicting "alternate control" trials directly comparing serotherapy versus sulfapyridine for the treatment of pneumonia *would* emerge over the next year, with the first appearing in the literature in March of 1940;[67] but before the force of such studies could be felt (and indeed, largely absorbing their impact), two factors would counter their determining preference for one agent over the other.

First, Merck officials seemed well aware that—in view of sulfapyridine's cost—they need not prove the sulfa drug's superiority over serum, but merely its near-equivalence and safety. Hence, with the FDA's impetus, their early efforts were geared toward rendering as many practitioners as possible familiar with the product—to demystify, in essence, through disseminating, the novel agent.[68] Their provision of samples to over 2,000 patients treated by 262 practitioners in

thirty-one states in the winter of 1938–39 was thus as helpful to them as it was to the FDA.[69] The course of many such "investigations" further rewarded their efforts. Some investigators, intending to compare serotherapy with chemotherapy, were forced to abandon their serum "control groups" in the setting of a paucity of pneumonia patients. The result was a simple demonstration of sulfapyridine's efficacy and safety.[70] Other investigators, despite initially intending to use sulfapyridine only for those cases in which serum was contraindicated, soon switched their primary treatment modality of all pneumonia patients to sulfapyridine alone as its efficacy and safety became apparent.[71]

By late spring, certain therapeutic rationalists had already taken the opportunity to warn of the expected impact of Merck's approach:

> "The medical profession will shortly be exposed to an intensive advertising campaign relative to the value of sulfapyridine in the treatment of pneumonia. Education of the laity in regard to the drug will progress many times faster than did serum education. . . . [Hobart Reimann] . . . regrets the commercialization of the drug at this time because he feels that it will gain too prominent a place in pneumonia therapy before its actions are sufficiently understood, and that valuable knowledge concerning serum will be ignored."[72]

Merck, however, continued its efforts, reporting in late 1939 (in a 46-page brochure reminiscent of the old Mulford "Working Bulletins") that samples to treat 18,000 patients had been distributed, with over 3,000 case reports returned and a gross mortality rate of 6 percent obtained.[73] Two years later, in discussing the historical amassing of evidence in favor of diphtheria antiserum, Finland would speak of the "sum total" approach, in which "abundant experiences from innumerable physicians more or less uniformly attest to the efficacy of serum."[74] Perhaps he would be influenced by what had transpired with the emergence of sulfapyridine for pneumonia. Before a single head-to-head alternate control trial with serum was reported, sulfapyridine would be deemed clinically effective (at least in comparison to historical controls) and relatively safe on a widespread basis. By the fall of 1939, the thoughts of some of serotherapy's foremost advocates were telling. Spink and Finland themselves, despite their persisting concerns, had drifted far from their positions of six months earlier:

> [Spink to Finland:] What is your feeling about sulfapyridine now? . . . The reason I ask you is that we are trying to formulate a hospital policy concerning its use, and also for my own knowledge.[75]

> [Finland to Spink:] We are, of course, using sulfapyridine a good deal and are finding it rather useful in many cases.[76]

Roderick Heffron, working for the same Commonwealth Fund that had funded the Massachusetts Pneumonia Study and Service under his direction, would go still further in writing to his former colleague, Elliott Robinson (of Massachusetts' state Antitoxin and Vaccine Laboratory): "I asked [Norman Plummer] about the use of the drug in statewide programs and he said flatly that he was sure it could be used with safety for such purposes. . . . I send this information to you for what it is worth and it seems to me a further indication of the way the wind is blowing."[77] Sulfapyridine's arrival was thus less a tornado sweeping away the rabbit warrens than a driving, steady breeze altering the murky therapeutic waters.

Still more critically, before the question of serum versus sulfa could even be answered, the very question was changed, as the potentialities of *combination serochemotherapy* captured the minds of many investigators and practitioners.[78] This turn of events, of course, further precluded any dramatic dissolution of serotherapy upon the sulfa drugs' arrival. As it became apparent that sulfapyridine was a bacteriostatic drug (i.e., capable of halting bacterial growth rather than destroying them directly, though its exact mechanism of action remained unknown), an updated military metaphor emerged: sulfapyridine, on its own, could only slow down the invader while the body's natural immunity would actually eliminate the pneumococcus.[79] As such, it seemed apparent to many that in the face of a foe as deadly as the pneumococcus, why always wait for natural immunity? Why not use combination therapy, especially in the setting of a large invasion (e.g., manifested as bacteremia or multilobar pneumonia) or a weakened host (e.g., pregnant women or the elderly)?

On top of such theoretical considerations, as early as January of 1939 at the New York Academy of Medicine conference on sulfapyridine, Bullowa could report on Edwin E. Osgood's in vitro human bone marrow studies (conducted with pneumococcal cultures supplied by Bullowa), in which a combination of rabbit serum and sulfapyridine caused complete phagocytosis (i.e., engulfment by macrophages, as discussed in chapter 2) of all pneumococci at forty-eight hours, in contrast to the use of either serum or drug alone.[80] And from the Rockefeller, Colin MacLeod could likewise describe, at the AMA meeting in May of 1939, the "synergistic" (i.e., more than merely additive) effect of antiserum and sulfapyridine exhibited by in vivo murine experiments with the dreaded type III pneumococcus.[81]

Clinicians were prepared to quickly translate such *a priori* principles and experimental findings to patient care;[82] and by mid-1939 a wide spectrum of roles

for combination therapy had been publicly put forth. From one end, Finland at Harvard considered that "a large percentage" of patients should benefit from both the synergy and potentially lessened toxicity (through the expected decreased amount of serum and drug required) of combination therapy.[83] More centrist others, like Francis Blake at Yale, turned the toxicity issue on its head, arguing for combination therapy only for the more severe cases, given that most patients less than sixty hours into the disease recovered with "adequate" dosing of either agent alone, making it "quite unnecessary to submit persons in this group, if treated with serum, to the discomforts and hazards of sulfapyridine therapy or *vice versa*."[84] At the far other end of the spectrum, Cook County Hospital researchers in Chicago argued that whatever pneumonia deaths remained after monotherapy were more likely to have been prevented by earlier use of one agent or the other than by combination of the modalities.[85]

Over the next two years, this variability in practice would continue to characterize the profession at large. At the one end stood such researchers as Charles Janeway and Paul Beeson, who—even when Finland himself would scale back on his suggested range for combination therapy—argued that *all* pneumonia patients should benefit from the increased efficacy and decreased exposure to sulfa drugs afforded by combination therapy.[86] Others would evolve from a stance of monotherapy toward one of combination therapy for an expanded proportion of patients over the course of the two years. John Brown, from University of California San Francisco, wrote to Finland in early 1941: "I recently organized our experience for the past four years for the county medical society. There were only 450 cases in which pneumococci were found in the presence of pneumonia, of which only 296 were primary pneumonia cases. However, these were fairly typical with a not very good looking fatality. This is the experience on our service of the county hospital. We are beginning to use more serum in the hope of bettering the results."[87]

Brown echoed Roy Thomas's own previous assertion before the California Medical Association in May of 1940:

> In a recent conversation with two men who have had wide experience and have written much that is considered authoritative on the treatment of pneumonia, each stated definitively that should he be so unfortunate as to contract pneumonia due to any of the lower types of pneumococci, he would wish to be treated with serum and sulfapyridine combined. Why, then, should we not use such combined treatment in every case where the cost is not prohibitive? I believe that we should, if the patient is not sensitive to serum, and preexisting renal or liver damage does not contraindicate the use of the drug.[88]

Yet Thomas's qualification—*where the cost is not prohibitive*—would reveal the crux of resistance to the use of combination therapy. Lawrence D. Thompson, who had initially advocated serotherapy over drug therapy at the AMA meeting in May of 1939, could, during the next pneumonia season, explicitly test and confirm—at least among the less-toxic patients—the oft-stated hypothesis that combination therapy could lessen the expenses (as well as the potential toxicities) of the dual agents through reduced dosages of each.[89] However, such reductions were only relative, and the therapeutic ideal of combination therapy remained, for many, a luxury rather than a right. The remarks of one Savannah practitioner after a presentation at his state medical society is particularly illustrative:

> I note in Dr. Hanson's report [on the use of sulfapyridine] that the two patients who died had positive blood cultures. Here the question comes up whether specific serum therapy would have been of any help. At the present time until clinical reports prove otherwise, I think that when a patient has a positive culture and if the patient can afford the serum, that both it and sulfapyridine should be given. One practical point about sulfapyridine is the comparatively low price. One hundred tablets, 50 [grams], cost about $5 to $6. This is enough for two average cases. Serum therapy would cost 5–10 times as much and is out of reach of the person of moderate means and the hospital that has a limited amount of money.[90]

As such, even in public presentations and reports, a form of lip service to the ideal of combination therapy emerged that was at variance with the easy tendency to administer sulfapyridine alone. One Dallas practitioner, for example, despite pronouncing before his state medical society that "judicious combination of sulfapyridine and specific serum represents the ideal treatment of pneumococcal pneumonia," nevertheless administered serum to only 13 out of 220 sulfapyridine-treated patients.[91]

To be sure, practitioners were more apt both to promote and use combination therapy under the auspices of the more generous state pneumonia control programs. As such, a key determinant in the use of combination therapy derived from decisions made at the level of state and local public health departments and medical societies.[92] In the heavily serum-supported state of Illinois, for instance, practitioners would continue to use serotherapy in marked excess of the norm nationwide (table 6.1).[93] In contrast, from New Jersey—where expensive serum provision was regulated far more stringently, and where Merck provided to the state enough free sulfapyridine in 1939 to treat 1,000 cases—came the observation that sulfapyridine had "greatly superceded" the more expensive, typing-center-dependent serotherapy.[94]

TABLE 6.1
Illinois Pneumonia Control Program Efforts, 1938–1942

Year	Total Number Patients Treated	Treated with Serum Alone	Treated with Sulfa Alone	Treated with Combination Therapy	Percentage Combined	Cost of Serum ($)	Cost of Sulfa ($)
1938–39	1,016	1,016	x	x	x	54,254 (derived)	x
1939–40	4,158	270	1,573	2,315	59.5	142,968	12,968
1940–41	7,132	187	3,908	2,801	41.7	167,840	12,855
1941–42	5,030	62	3,076	1,753	36.3	102,845	4,582

Source: 22nd Annual Report of the [Illinois] Department of Public Health, July 1, 1938 to June 30, 1939, 69; 23rd Annual Report of the [Illinois] Department of Public Health, July 1, 1939 to June 30, 1940, 45; 24th Annual Report of the [Illinois] Department of Public Health, July 1, 1940 to June 30, 1941, 224; 25th Annual Report of the [Illinois] Department of Public Health, July 1, 1941 to June 30, 1942, 64.

However, the states' roles were far from absolute in determining the decisions of providers, leaving broad intrastate variability. For example, in New Mexico—where both serum and sulfapyridine were provided for the 1940–41 season—29.1 percent (61/209) of treated patients received combination therapy from fourteen stations spread over nine cities; yet only one patient out of forty-nine received serum within the purview of Carlsbad's two stations.[95] And in Illinois' far larger program, the carefully tabulated county data of 5,030 patients from the 1941–42 program reveals a range of combination-treated patients from 25–77 percent among counties with greater than twenty treated cases, a range that only shrinks to 25.4–75 percent among counties with greater than one hundred treated cases.[96] While still-unknown local forces apparently led to such spread, other patterns were more easily discernible: when only 29 percent of Chicago residents received combination therapy, compared with 45 percent of patients throughout the remainder of the state, the contribution of the pro-monotherapy Cook County investigators was clearly visible to state administrators.[97]

Lysis: Therapeutic Transformation

Hope that just such potential contingencies of usage would yield to more "rational" and general determinants of care continued to be prominently expressed. By early 1940, given the prevailing variation in usage of combination therapy—and in the absence of any consistent data favoring serum, sulfa, or combination therapy for pneumococcal pneumonia as a whole or for particular serological or epidemiological subsets—an editorialist in *JAMA* professed both the profession's ignorance and its hopes for clarity: "In view of the almost equally enthusi-

astic reports regarding these new therapeutic agents, the practitioner is confronted with the problem of choosing the one or the other or the combination of the two. Studies relative to their comparative effectiveness have thus far been few. . . . The relative value of the two methods and the indications for their employment, as well as for the combined use of the two, await further clinical studies."[98]

The subsequent year, however, witnessed a retrenchment in serum usage—certainly as a single agent, and even as a component of combination therapy—that outstripped any negative clinical data *per se*. As physicians became still more familiar with sulfapyridine, published calculi of administration began to permit its use in the absence of laboratory monitoring (even if only when such monitoring was absolutely precluded secondary to remoteness from a large hospital or laboratory).[99] And as more physicians became comfortable using the sulfa drugs for pneumonia, many of their patients seemed to be getting better with use of the drugs alone, setting in motion a self-reinforcing cycle. Wrote Yale Kneeland, from Presbyterian: "This is a controversial subject about which it is impossible to be dogmatic. There is evidence that the beneficial effects of the drug are enhanced if it operates in the presence of specific antibodies. On the other hand, it has been our experience that the *great majority* of patients with lobar pneumonia will recover promptly on drug treatment alone, thereby making the costs, the complications, and the hazards of serum therapy unnecessary."[100] Equally important, the playing field itself continued to change, as physicians' attention soon turned to subsequent sulfa derivatives (such as sulfathiazole), which seemed better tolerated.

Combination therapy—still idealized on a priori principles and without any direct clinical blows to its status—was thus losing ground.[101] By September of 1939 Finland, while still holding out combination therapy as a therapeutic ideal, was willing to save such an aggressive approach for the more worrisome cases: those with positive blood cultures, those with multilobar or type III infections, patients over the age of forty, and pregnant women. For all others, sulfapyridine could be administered (if not contraindicated), with serum added only if "definite clinical improvement" had not been observed within 18–24 hours.[102] And by the spring of 1940—after another winter's experience—he had restricted his scope for combination therapy to those bacteremic patients *over the age of fifty or with moderate to large colonies in culture,* to those over *sixty* years of age, and to those failing chemotherapy after *24–36* hours.[103]

Finland was perhaps the most esteemed authority on pneumonia in the country. Tellingly, though, he was becoming (along with the similarly prominent Bul-

lowa) more of a therapeutic outlier as the burden of proof became the responsibility of the supporters of the expensive combination therapy.[104] Representative of the resultant vagueness, by May of 1940 Kneeland at Presbyterian reserved combination therapy for "maximally severe cases," with the qualification that "it is a little hard to define this group precisely."[105] A Nashville practitioner advocated combination therapy "in certain selected instances," while Francis Blake at Yale reserved it for "late, severe cases presumed to be bacteremic."[106] By the fall of 1940, Perrin Long and John Haviland at Hopkins, who had administered combination therapy to 23 percent (43/190) of their pneumonia patients the previous year, expected only 10–15 percent of future patients to require combination therapy—less "if in the future specific treatment is started earlier in the course of the disease."[107] Hobart Reimann, at Jefferson, chose the lower boundary of 10 percent in his own estimation, whereas Finland clung to the upper boundary.[108]

Prior to this time, studies comparing sulfa monotherapy with combination therapy had been both limited and conflicting. Although a small study of fifty young patients at Norfolk Naval Hospital had revealed no benefit (survival or otherwise) to combination therapy over sulfapyridine alone,[109] Harry Dowling's post hoc analysis of 162 "alternated" patients at Gallinger Municipal Hospital had seemed to point to the survival advantage conferred by combination therapy for those over the age of forty.[110] In May of 1941, though, Norman Plummer's group at Bellevue published their results concerning a remarkable 607 pneumonia patients alternated between chemotherapy and combination therapy over the course of the preceding two years. Not only did they derive overall mortality rates of 11.1 percent for the "drug only" and 14.6 percent for the combination groups, but they found that neither bacteremic patients nor those of any particular age group seemed to benefit from the addition of serotherapy.[111] Within three weeks, at the annual session of the American Medical Association, Dale Stahle, director of the Pennsylvania Department of Health's Division of Pneumonia Control, would confirm such findings through a retrospective analysis of the 15,000 pneumonia cases reported to his state over the preceding two years. Not only had combination therapy failed to better chemotherapy alone among the bacteremic or elderly, it had likewise failed to show additional benefit among those with particular pneumococcal types or concurrent disease.[112]

For both Plummer and Stahle, such findings represented the triumph of clinical data over "theoretical" and experimental expectations, an advance paralleled by the impeachment of such theory itself when Bellevue's William Tillett presented before the Association of American Physicians his finding that in the era of chemotherapy, the presence of demonstrable type-specific antibodies in the

serum seemed neither necessary nor sufficient for recovery.[113] As Russell Cecil—serum's original champion at Bellevue—summarized, in the wake of Tillett's presentation and Plummer's data: "There seem to be very good arguments to support serum therapy in bacteremic forms of pneumonia, but when the problem was attacked by statistics, we are surprised to find that the death rate was actually lower in the group that receives chemotherapy alone, so I would venture to say that if serum therapy in pneumonia is not dead, it is at least moribund."[114]

But such announcements of serum's impending demise were greatly exaggerated. While Plummer himself continued to advocate the addition of serotherapy as a backup to those patients who "fail to respond satisfactorily within twenty-four to forty-eight hours to drug therapy,"[115] Stahle not only advocated such backup usage, but backed up himself, hinting at the limits to the generalizability of his data in admitting that "clinical judgment is essential" and advocating for combination for "those patients extremely ill and in whom prompt recovery is necessary."[116] Moreover, as will be discussed at length in chapter 7, such prominent and persistent serum enthusiasts as Plummer's onetime co-authors, Jesse Bullowa and Max Finland, attacked not only the generalizability but the intrinsic validity of such studies on account of potentially unacknowledged bias in selecting more "severely stricken" patients to receive combination therapy.[117] Nonplussed by Plummer's and Stahle's results, Bullowa would still counter at the 1941 AMA session: "Serum therapy reduced the gross mortality rate from pneumonia one half; chemotherapy reduced it another half. It is this quarter or some of it which may be benefited by the combination, adding augmented resistance to reduction of virulence."[118] Encountering, in some quarters, a far different form of resistance, Plummer's results would serve as a litmus test among preexisting therapeutic currents as much as a driving force in itself.

For those whose economic disinclination to use combination therapy outweighed theoretical considerations, Plummer's data justified serotherapy's elimination. For example, a rural Minnesota practitioner would write in *JAMA* both of his pride in having used serotherapy (and thereafter combination therapy) as efficaciously as could any urban practitioner and of his subsequent enthusiasm to drop serotherapy as soon as "reports in the literature . . . indicated that the lowest mortality was often obtained by chemotherapy alone."[119] Similarly, delivering a respectful eulogy for serotherapy, an editorialist in the *North Carolina Medical Journal* wrote in June of 1941 of Plummer's "iconoclastic" results:

> Should these results receive widespread verification, as seems probable from the unimpeachable character of the testimony, a great advance will have been made in

> the therapy of pneumonia. Serum treatment is complicated and expensive and, though one which has cost so much in both labor and money, yet no one will forget the pioneer workers, especially Rufus Cole and his colleagues at the Rockefeller Hospital, who first elucidated so brilliantly the pneumonia problem. Their studies aid us in the appreciation of what is perhaps the most spectacular and fruitful therapeutic advance in the history of medicine, and, while rejoicing in the new, let us remember the old with gratitude.[120]

Yet a sufficient supply of academicians and general practitioners remained willing to assail such "unimpeachable character" to maintain spirited support for combination therapy.[121] From Hopkins came an attack on the applicability of Plummer's findings on account of the apparently meager amount of serum administered per patient,[122] a verbal thrust accompanied by Harry Dowling's criticism of the delayed timing of such serum administration.[123] Finland continued to notify the profession that it was still "generally agreed that specific antipneumococcus serums are useful in the treatment of the most severe cases and those having the worst prognosis."[124] And segments of the profession were still listening—especially when the pneumonia control programs were echoing such sentiments. In both Iowa and Illinois, for example, combination therapy continued to exceed even Finland's expectations. Roderick Heffron, while viewing Iowa's glass syringes as half-empty, implicitly revealed to Finland in March of 1942 the extent to which serum was still being administered:

> A few weeks ago I was in the middle west and spent a day or so in Des Moines, Iowa, talking with the State Department of Health people there about their pneumonia program. They are treating several hundred cases of pneumonia a year throughout the state and are supplying serum and various of the sulphonamide drugs for use free for patients who are unable to pay for such preparations. Although they have numerous typing stations scattered around the state, only about 40 percent of all the cases they have records of are being typed. Somewhat more than half the cases treated are being given some serum and the Health Department group feels keenly that typing and serum therapy are not sufficiently used over the state.[125]

Iowa's apparent serotherapeutic restraint, moreover, was to be contrasted with the persistent use of serum in Illinois in the post-Plummer era. As Heffron continued: "[O. H. Robertson] says that the Illinois state pneumonia program is going great guns and that they are using quite a lot of serum. He fully appreciates the importance of coming to a sound conclusion as soon as possible on the usefulness of drug alone, as compared with treatment with both drug and serum."[126]

Indeed, for the first half of 1942, 36.3 percent of Illinois cases reported to the state pneumonia control program (calculated to represent half of all pneumonia cases in the state) would *still* receive such combination therapy, identical to the percentage treated during the previous six months.[127]

Thus, when Chester Keefer (Finland's former colleague at Boston City Hospital and soon to become the nation's "penicillin czar" overseeing the distribution of the antibiotic) heard William Kelley (of the Medical College of South Carolina), in November of 1941, implicitly dismiss by essentially ignoring combination therapy at a presentation before the Southern Medical Association, he politely countered that "this is a subject that is exciting a tremendous amount of discussion at the present time, and you find interested investigators who are quite undecided whether or not the use of serum and chemotherapy will improve the present mortality statistics."[128] Kelley's counter-response, however, once again revealed the degree to which the continued self-reinforcement of accumulated individual monotherapy cases, as much as any alternate control study, strengthened practitioners' reliance on up-front monotherapy:

> Perhaps we have gone too far in leaving serum therapy out of first consideration in the treatment of pneumonia. However, this has become our practice for the reason that serum therapy, when used generally, proved a considerable financial burden, and also, we have grown to place a great deal [of], perhaps too much, confidence in the use of the sulfonamide drugs. It is possible that the amazing results which usually follow the use of sulfonamide drugs have lulled us into a certain amount of complacency in not giving serum therapy at the start of treatment in gravely ill cases, but I do not believe our results show detriment from that source.[129]

Equally striking, Kelley's limited use of backup serum for those "failing" to improve (he had used combination therapy in only 7/213 patients) belied the expectation that a significant fraction of patients would require such rescue (in 1943 Arthur Frisch and his colleagues at the Detroit Receiving Hospital would find that 30 percent of patients had failed to defervesce by forty-eight hours), again pointing to the lip-service advocacy of backup serum among those disinclined to its usage.[130] Norman Plummer defended such practice patterns still more emphatically before the Indiana State Medical Association ten months later, in his own continued submersion of serum:

> On the basis of our findings we concluded that serum had no role, except in the patients who could not tolerate the sulfonamide drugs and those who did not respond to them within twenty-four to forty-eight hours. How often do such cases occur?

> They occur very infrequently. At the New York Hospital, where we have been well trained in the use of serum, serum has been used three times in the past three years. In private practice I have used serum one time in three years, and in no case in my personal experience, in the hospital or outside, has the use or disuse of serum been the deciding factor in the outcome.[131]

The scattered pro-combination counter-responses over the next two years repeated the old warnings against such apparent complacency. Finland—finally declaring in 1943 that neither bacteremia, number of affected lobes, nor age represented absolute indications for combination therapy—retreated to the vague pronouncement that "the indications for the use of serum are difficult to define, but, in general it should be given to the very sick patients and to those who fail to respond to adequate doses of sulfonamide."[132] Bullowa remained unbowed, continuing to level at any finding of increased mortality among combination-treated patients the counterfactual claim that the patients who received combination therapy were more stricken and would have done still worse had combination therapy not been administered.[133] In the midst of such wrangling, leaders from both sides of the debate continued to hope for improved laboratory and statistical methods to assist in the "rational" application of combination therapy.[134]

Such a rational climax, however, would once again remain an unattainable ideal as antipneumococcal serotherapy's denouement was already being played out in the context of four critical—if less glamorous—factors. First, serotherapy's foremost advocates had largely deserted the cause or died by 1943.[135] Second, in contrast to the high hopes that the advent of World War I had inspired for the testing of serotherapy, the advent of World War II—while boosting Lederle's sales of antipneumococcal antiserum to the federal government—offered only the depletion of the pneumonia control programs, as the military made no large-scale attempts to test combination versus monotherapy. (Its most notable pneumonia studies at this time would instead center on prevention via the pneumococcal polysaccharide vaccine, as will be described in chapter 8). Indeed, in the absence of such centralized studies, "remarkable variation" characteristic of the use of combination therapy nationwide likewise characterized its use in the military, as uncovered in a Professional Service Division survey in 1944.[136]

By that point, moreover, a third critical factor—the timely advent of "atypical," or "viral," pneumonia—would have rendered such centralized approaches still more problematic. First "described" by Hobart Reimann in 1938, the disease was characterized by the gradual onset of fever, sweats, a nonproductive cough, and an apparently diffuse pneumonitis.[137] It had become more prevalent than lobar

pneumonia itself during an epidemic between 1941 and 1943,[138] with pneumonia researchers themselves similarly flocking to the disease.[139] And in considering the disease from a therapeutic standpoint, the specificity of the serums remained their own undoing in the setting of the apparent absence of bacteria, let alone pneumococci, in the sputum of affected patients.

But antipneumococcal serotherapy's ultimate dissolution came with a fourth factor: the advent of penicillin, an agent that could assume all of serum's former roles, whether in combination with the sulfa drugs or as backup. On November 4, 1943, William Tillett reported before the New York Academy of Medicine the treatment of forty-six pneumonia patients with the apparently minimally toxic drug.[140] The implications for serotherapy were made evident by Plummer himself at the meeting: "It is reasonable to suspect that in the future sulfonamide-resistant infections and drug-sensitive individuals will play a much greater role in pneumonia; but I dare say that after hearing Tillett's report, you will agree that when penicillin becomes generally available this drug and not serum will furnish the answer to this problem."[141]

In the army, antipneumococcal serum was discontinued from active drug lists on May 15, 1944;[142] and Finland himself would make such a replacement explicit in his presentation on the treatment of pneumonia in *Medical Clinics of North America*.[143] By late 1944, Bellevue's Committee on Drugs and Formulary recommended the deletion of antipneumococcal serotherapy from the hospital's formulary in the same missive in which sulfapyridine's own deletion was announced.[144] The same year witnessed Lederle's final commercial serum sales;[145] and by the following year, the state of New York—where so much of antipneumococcal serotherapy's evolution had taken place—ceased production of the specific.[146] Nearly a decade after the discovery of the sulfa drugs, antipneumococcal serotherapy had thus at last disappeared, the product of a gradual lysis of roles rather than of any particular crisis of efficacy.[147]

A "Modern" Revolution

The Limits and Uses of Controlled Clinical Trials

The tempo of the antipneumococcal chemotherapeutic "revolution" reflected the competing impacts of a number of clinical and economic forces. Chapter 6 has already emphasized the degree to which the pragmatics of practice—the inertias, implementation infrastructures, and variously defined costs of the two respective agents—would shape such a transition. In short, it has emphasized the degree to which such fine contingencies must be recognized in describing particular evolutionary changes in medical practice.

This chapter will instead delineate the impacts of an emerging controlled trial ethos and the pharmaceutical industry itself on such a transition. It is my expectation that more universal, "modern" therapeutic influences (and the dilemmas they fomented) will become readily apparent in addition to further contingencies unique to the antipneumococcal therapeutic transition of the late 1930s and early 1940s. Situating such clinical epidemiological and pharmaceutical industry forces within the antipneumococcal chemotherapeutic "revolution" thus offers a unique opportunity to evaluate further their own evolution in this century as well as to lend further nuance to the overall depiction of the antipneumococcal chemotherapeutic revolution per se. And much as I have attempted to demonstrate that the therapeutic specific considered characteristic of post–World War II medicine had already been entrenched to a large degree in the decades prior, so will I now attempt to emphasize the degree to which many of the so-called modern dilemmas concerning "rational" clinical decision making and the impact of commercial forces likewise had their origins prior to World War II.

Situating the Controlled Clinical Trial

In fleshing out the evolution of the clinical trial in the United States in the twentieth century, Harry Marks, in *The Progress of Experiment* (1997), offers a pow-

erful corrective to what he has labeled "transhistoric narrative[s] of antecedents" that (as noted in chapter 3) provided the most tenuous of links, for example, between Fibiger's introduction of the alternate control study in 1898 and the flourishing of the randomized control trial in the 1940s and beyond.[1] Instead, Marks situates the controlled clinical trial amidst reformers' attempts to inculcate rational medical practice throughout the twentieth century. However, while acknowledging pre–World War II concerns regarding the methodology of controlled studies, Marks chiefly credits the pre–World War II reformers with making such key *structural* changes in the approach to a rational therapeutics as the formation of therapeutic reform committees and inter-hospital collaborative clinical studies. The pre–World War II era remains for him largely the domain of personal authority over methodology, rendering the "triumph of statistics" a post–World War II affair;[2] and it is this latter characterization that I will explore here.

Marks certainly acknowledges prewar methodological concerns.[3] Nonetheless, he leaves the bulk of such consideration about the fundamentals of "managing chance" to the postwar reformers, themselves rattled by the difficulties of wartime penicillin evaluation (in the context of disease, patient, and therapeutic variability) and inspired by the advent of randomization as formulated by Ronald Fisher, practiced by A. Bradford Hill in his evaluation of streptomycin for tuberculosis in 1948, and preached by such statisticians as Hill and Donald Mainland in the 1950s.[4] Marks further ascribes to Hill and the post–World War II era such concern regarding bias as would lead to the advent of randomization and "blinding" in the streptomycin trials;[5] and to subsequent generations concern regarding the actual generalizability and applicability of study findings to individual patients.[6]

My contention with such a characterization of the pre–World War II era, however, is twofold. First, in minimizing the concerns of the pre- and peri-war era, one runs the risk of neglecting the degree to which present-day clinical epidemiological "dilemmas" had already been recognized and publicly displayed, thus potentially forfeiting the opportunity to better understand their origins. Second, minimizing the pre–World War II debate and developments leads to a subtle progressivism and, perhaps, hubris regarding contemporary decision making. Barron Lerner, for example, cleverly "revisited" the emergence and spread of the sulfonamides in the relative absence of rigorous clinical data in order to divine the implications of the FDA's loosening of regulations in the 1990s in its efforts to foster faster drug approval and utilization. As he summarized:

> By releasing medications before completion of definitive studies, the new, less stringent FDA regulations place the interests of current patients ahead of the long-term

> concerns of science and future patients. As a result, decision making by doctors and patients is becoming more autonomous, but it is also, as Edgar and Rothman warn, becoming less informed. They foresee "more hunches, more variety, ultimately more 'schools' of medicine." In this sense, modern practitioners will be operating in an atmosphere similar to that experienced by their counterparts 60 years ago.[7]

I would counter that in many respects, subsequent practitioners have never fully divested themselves of the dilemmas of sixty years ago, perhaps rendering their depiction all the more familiar and startling.

Certainly, this section represents more a modification than an impeachment of Marks's and Lerner's presentations on the state of clinical epidemiological sophistication during the late 1930s and early 1940s. As the Commonwealth Fund's Lester J. Evans wrote in 1934 of Roderick Heffron's planned treatise on pneumonia (supported, like the Massachusetts Pneumonia Study and Service itself, by the Fund): "It is lacking in the type of dogmatism which I believe the average medical man expects. . . . There is possibly too exclusive use of statistical tabulations and summaries. All in all, I do not feel that the book as at present written . . . is just the thing for 'lowbrow' medical reading. It would be too much of a struggle for the average doctor who reads casually to get the meat."[8] And as described earlier, given the ease and minimal expense of sulfa administration, few practitioners or their patients were content to wait for controlled trial data to begin implementing the sulfa drugs for pneumonia.[9] The consequent effect on practitioner and patient behavior would even be felt by those attempting to enroll patients in clinical studies, as when William Spring passed along to Maxwell Finland in late 1939 and early 1940 the lamentations of the New York investigators who "were having trouble getting patients—the practitioners wanted to give the drug at home."[10]

Yet not all local practitioners behaved in such fashion.[11] And a core of clinical and bench scientists would take it further upon themselves to inform their medical brethren to await such experiments at this time. Some, as mentioned previously, would emit gentle calls in the spring of 1939 for the patience to evaluate the sulfa drugs over several pneumonia seasons in order to remove the confounding influences of disease variability.[12] Others, however, were less ginger in their assessments of researchers' hastily produced, poorly controlled studies, and of clinicians' potentially inane acceptance of such studies. Robert Kilduffe, speaking before the Medical Society of New Jersey in June of 1939, would remark of the gathering accounts of treated sulfapyridine cases: "What is gravely needed is not statistics, but the accumulation of accurate and *critically analyzed* statistics derived from the *careful and critical analysis of carefully controlled* studies."[13]

Kilduffe at least perceived a silver lining to the clinically cloudy "sum total" approach (to use Finland's term, as discussed in chapter 6), for it would potentially "bring to light all the sooner the contraindications, the complications, and the undesirable aftermaths which may exist."[14] However, Jesse Bullowa, in his *JAMA* letter written with Finland and Norman Plummer in early 1939, sought to minimize the therapeutic foolishness and damage that could accrue before "carefully controlled observations" had revealed the proper status of sulfapyridine and serum:

> In recent years many agents, chemical, physical, and biologic, have been recommended for the treatment of pneumonia. In each instance the early experiences were brilliant, marked reductions in death rates and striking therapeutic responses being noted. . . . In most instances the early reports considered too few cases and did not take into account the most important factors influencing the mortality in this disease. Individual cases or small groups of clinical results were reported with great enthusiasm. . . . During the past year sulfapyridine has been introduced into the therapy of pneumonia in England, and this drug is now having a number of clinical trials in this country. The earliest clinical reports and subsequent ones from England were made without proper controls and the data presented were grossly inadequate for any evaluation. Similar reports have been made recently at various medical meetings and even greater publicity has been given this drug in the lay press and in radio reports in this country. Unfortunately no published reports have yet appeared with any data from which the value of this drug can be assessed. . . . If evaluation in experimental animals under standard and controlled conditions is difficult, it is all the more reason for extreme caution in reporting results in human beings."[15]

In other words, therapeutic rationalism demanded that American clinicians elevate themselves—from their patients, from the media, and from their own collective past.

For the three clinician-scientists, statistical concerns may at the time have chiefly served the practical need to forestall the potential widespread abdication of serotherapy.[16] Yet the three men would remain at the forefront of the clinical epidemiological transition accompanying the continued development of antimicrobial specifics; and the remarkably divergent approaches to "carefully controlled observations" they would take over the next several years—especially as applied to the merits of monotherapy versus combination antipneumococcal therapy—serve almost typologically to demonstrate contemporary concerns regarding the perceived intrinsic validity, as well as the applicability to broader pa-

tient populations (or what would eventually come to be called "internal" and "external" validity, respectively), of controlled clinical trials themselves on the eve of World War II.[17] Still further, much as it serves to orient more precisely the ultimate post–World War II dominance of statistics in medicine and permit an appreciation of persisting tensions, an appreciation of such debate among "therapeutic reformers" offers additional insight into the specifics of resistance to the antipneumococcal chemotherapeutic revolution.

Finland and Challenges to Internal Validity

For Plummer, the controlled clinical trial—epitomized by his study of the chemotherapeutic versus serochemotherapeutic treatment of pneumococcal pneumonia[18]—served as a final arbiter, superceding both theoretical expectations and clinical impressions. Regarding monotherapy versus combination therapy, he recounted: "At Bellevue Hospital, we studied this problem statistically, believing strongly at the start that combined therapy was superior, and desiring to find out the degree of its superiority. . . . At the conclusion of the study we were surprised to find no appreciable difference between the two groups."[19] As such, controlled clinical studies—with due precautions—approached the purity of the rigorously controlled laboratory experiment: "The plan we had in mind from the start was to handle the series as though the patients were being treated in two different hospitals. On the shelves of the one hospital there was a supply of the sulfonamide drugs, and on the shelves of the other there were both sulfonamide and serum. Everything else was the same for the two groups of cases. In each series the effort was made to obtain the results possible under the circumstances of the experiment."[20] Rufus Cole's concerns (as discussed in chapter 3) regarding the transposition of the controlled laboratory ethos to the clinical realm, it would seem, had been put to rest four years after Cole himself had stepped down as the director of the nearby Hospital of the Rockefeller Institute.

For Finland, however, the application of the controlled clinical trial—while a heuristic ideal—remained beset by a host of ethical and epistemological nettles; and his evolving concerns serve as a touchstone for contemporary doubts regarding the incipient statistical revolution. Ethically, there persisted the conundrum of withholding a medication considered effective a priori (whether based on theoretical or experimental considerations) from a control group. As he remarked of twentieth-century attempts to verify the widely acknowledged (though not unequivocally proven) efficacy of diphtheria antitoxin through rigorous alternate control trials: "As soon as most persons are convinced that the remedy is

effective, it becomes impossible for any human therapeutic experiments to be carried out to a logical conclusion."[21] Such concerns, of course, rested on neo-Colean doubts regarding the inherent superiority of controlled clinical trial data to that derived from other experimental sources in the first place. The earliest antipneumococcal antiserum studies by Locke and the Boston City Hospital Pneumonia Service, for instance, had first convinced Finland of the difficulties of "managing chance" (to use Marks's term) in clinical studies because the apparent inefficacy of type I antiserum seemed, upon Finland's own later review, to have been confounded by a twofold greater incidence of a priori bacteremia in the serum-treated cases.[22] And even by 1941, as studies became ever larger and standards of deviation smaller, Finland remained uneasy with the role played by chance in clinical studies.[23]

Such fundamental statistical uncertainty, moreover, was further plagued in the clinical setting by the messiness of the data itself, as human patients refused to accept their roles cleanly in any therapeutic experiment. As Finland reflected of his own first alternate control studies of antipneumococcal serotherapy: "Serum was given to alternate cases of each type as soon as the type was determined. From the very start it became obvious that such controls were only self-deluding. We were confronted with patients in whom the type was determined after the patient was already dead, and others who were moribund when the results of the typing became known."[24] As such, Finland felt that in medicine as elsewhere, statistics could lie, lamenting in his 1941 review of antipneumococcal controlled clinical trials: "I hesitate in this discussion to introduce statistical analyses, since this review is concerned with attempts to demonstrate unequivocal value in clinical experiments, and it has always seemed to me that when such value is not definitely apparent, the application of statistical analyses serves only to salve the conscience of the person who presents the data."[25] Instead, he countered with a deterministic methodology dependent—rather than on comparisons of mortality tables—on individually rationalizing each of an expected efficacious therapy's failures.[26] Chance would not have to be managed, since failure could be explained away in each case. Marks has hinted at the determinism that medical statisticians would have to counter in the post–World War II era,[27] and Finland had articulated such a determinism before the profession at large.

Finland's defense of (or retreat to) determinism, however, was fueled by a final—and critical—source of unease regarding the validity of antipneumococcal trial data: the potential for unconscious selection bias in the assignment of patients to treatment groups. Finland had noted as early as in his review of the studies performed by residents at Boston City Hospital in the 1920s (studies that had

apparently suggested the efficacy of antiserum in the treatment of types 1 and 2 pneumococcal pneumonia) the "disturbing feature" of decreased mortality among type 3 and 4 cases who had received only bivalent (types 1 and 2) serum.[28] In uncovering the source of such results, Finland had become still more piqued: "It was assumed that the successive residents treated alternate cases as long as they had serum, discontinued their experiments when no serum was available, and kept records only during the time that the experiment was going on. . . . [However, upon] analyzing the data on this point, it was easily shown that the so-called 'control cases' had a definitely unfavorable age distribution. This was also true of the distribution according to the stage of the disease. Among the serum-treated cases, a larger percentage were admitted early in the disease, and fewer late cases were included."[29]

In other words, perhaps the emerging knowledge that early-treated cases would respond better to serum had biased the subsequent selection of cases by the residents. Conversely, nearly two decades later, it had become obvious to certain investigators that preferential usage could bias *against* combination therapy vis-à-vis monotherapy in any retrospective analysis of a non-controlled study, given that theoretical expectations would bias practitioners toward the use of combination therapy for the sickest patients (as discussed in chapter 6 with respect to Bullowa's attack on the Pennsylvania Public Health Department data).[30] While Bullowa, for instance, suggested that truths might emerge with ever-finer post hoc stratification, Finland was less hopeful: "I have thought a good deal about the interpretation of data such as might be available from mass statistics obtained by public health workers. It is difficult for me to escape the impression that accurate evaluation of these data would be extremely difficult. Regardless of how conscientiously people use specific serums, it is hard for me to see how physicians who use the chemicals now available could help having an entirely different class of patients treated with the combination of drug and serum. The problem is one of evaluating the samples which are to be compared."[31]

Such retrospective reservations may hardly have been unique to Finland, but he saved his harshest words for an attack on bias in the most hallowed of settings: the contemporary alternate control trial. Concerning Plummer's study, he had become wary upon noting the grossly uneven distribution of several pneumococcal types between the two groups, despite the "strict alternation in type stressed by these authors."[32] Finland could wax cynical when provoked.[33] But with respect to the researchers at Bellevue, he was understanding, even charitable: "Some unconscious selection on the part of the authors played an important role in the inclusion of the poorest subjects among the serum recipients. This is only a natural

occurrence, since there is always a tendency to give to the patients who seem the most severely ill the benefits of any remedy that is known to be effective."[34] Whatever the motive, though, the erroneous results produced were equally dangerous, as he publicly (and remarkably frankly) concluded of Plummer's study: "The conclusions drawn by these authors may or may not prove to be correct, but one cannot help believing that the results as presented are not only inconclusive but even grossly misleading."[35]

Finland's courage in rendering such a proclamation was further demonstrated by his sending a copy of it to Plummer prior to publication; and Plummer's parry would appear in the same issue of the *Journal,* representing, as it were, an eloquent defense of the alternate control trial ethos. For Plummer, the management of chance by statistical means was to be embraced (again, to use Marks's terminology), rather than feared. As he responded to concerns raised by Finland regarding the unequal distribution of patients dying within twenty-four hours of admission: "This was exactly the way the series turned out, and it shows how the laws of chance operate in such a study."[36] Regarding the messiness of the data itself, Plummer justified what in modern parlance would be termed an "intention-to-treat" approach in his assignment of patients to one group or another (as with, for example, those patients dying within twenty-four hours, or conversely, those responding to sulfapyridine alone before ever requiring—or receiving—serotherapy), so as to minimize any role for the researcher to manipulate the data a posteriori.[37] But Plummer would save his most spirited reply for the accusation of unconscious selection bias: "We avoided such a possibility by taking a number of precautions. There were a number of physicians treating the patients, and they had nothing to do with the alternation of the cases. This was done in the laboratory by the technicians, who again had no knowledge whatever of the clinical condition of the patients. Furthermore, the serum was kept in the laboratory and delivered to the ward when a serum case was discovered. On this basis, how there could have been a conscious or unconscious selection, I am at a loss to explain."[38]

Finland remained unconvinced, either unable or unwilling to accept such explanations. Regarding Plummer's denials of bias, he would remark to Roderick Heffron in early 1942:

> Even in the case of a single large hospital, as for example in the Bellevue study where they tried very hard to alternate cases, the end result as the data are presented indicates to me that such alternation was not carried through, and it is easy to tell from conversations with interns who were working in this hospital at the time that this impression is justifiable. From the natural reluctance of people to use the expensive,

> time-consuming or care-requiring therapy, it is obvious that serums will undoubtedly be reserved for the worst risks. It is not always possible to detect this choice where a double treatment is employed since the first therapy—in this case sulfonamide—eliminates most of the worst cases which will recover, leaving those who are most likely to fail to respond in the group which receives serum. I have struggled with this question quite a good deal, . . . and have not been able to figure out any way of answering it without a set-up which is hardly justifiable on the basis of what can be learned from such a study.[39]

Indeed, statistical disdain, if not statistical nihilism, would continue to pervade his thinking throughout this time.[40]

Such protests were not voiced in a vacuum, given Finland's prominence. For example, Robert Petersdorf, in the pages of *JAMA* in 1984, would label Finland's 1941 study of sulfadiazine (likewise published in *JAMA*) a "classic," discussing it in the "landmark perspective" section of the journal.[41] Published three weeks after Plummer's aforementioned study (a juxtaposition apparently lost on Petersdorf), Finland's article, Petersdorf said, "set a style for clinical investigation that became the gold standard for how antibiotics should be scrutinized, both in the laboratory and the clinic, before they could be let loose on the profession and the public."[42] And Finland's methodology, apparently, would be passed directly to countless disciples in the ensuing years:

> Max Finland and his hard-working group of fellows . . . studied literally every new antibiotic as it appeared, each in the same meticulous way. Over the years, they published hundreds of articles. If a new antibiotic did not have the Finland stamp of approval, it had little chance to make it and for good reason. Considering the many quick and dirty articles that have populated the antibiotic literature over the years, Finland's group served as the beacon of quality that maintained a standard for the whole field. . . . [Moreover], he inculcated his standards and his work ethic into two generations of clinical investigators who have carried out the major studies in antimicrobial therapy in this country.[43]

Yet interestingly—and not surprisingly—the sulfadiazine study was not an alternate control trial, but rather the epitome of Finland's approach in 1941. As Finland explained at the time:

> The laboratory evidence that sulfadiazine has a wide range of effectiveness, the relatively high concentrations of this drug that are so readily maintained in animals and in human beings and its low toxicity which became apparent from the first clinical trials led us to attempt an evaluation of its therapeutic effect in all cases of bac-

> terial infections in which sulfonamides might prove useful [amounting to 178 pneumococcal pneumonia patients, 138 non-pneumococcal pneumonia patients, and 130 patients with a variety of other infections, from upper respiratory tract infections to pyelonephritis]. Sulfadiazine was therefore used as the only sulfonamide drug in five of the medical wards beginning November 1 [1940] and in three additional wards beginning January 1 [1941].[44]

And after obtaining a 10.7 percent mortality rate among pneumococcal pneumonia patients (16 of whom received serum as well), Finland turned to a deterministic explanation of the nineteen fatalities observed (only two of which he ascribed to the pneumococcal infection itself).

Petersdorf positivistically pardoned Finland's lack of use of alternate controls as a default to the obvious, again reinforcing a rigid pre- and post–World War II epistemological dichotomy: "The large number of patients studied in a brief time permitted a comparison with a similar group of patients studied in previous years with serum therapy or other sulfonamides and also eliminated the need for randomization—for which there really could not be an ethical excuse in patients as ill as these, even in 1940, when this matter did not have as high a priority in clinical research as it does now."[45] Yet as shown above, Finland's opposition reflected a self-conscious suspicion of the internal validity of the alternate control study, publicly setting forth the very quandaries future clinicians and statisticians would have to address in the ensuing "revolutionary" decade and beyond as well as preventing a clear acceptance of Plummer's dismissal of antiserum in particular.[46]

Bullowa and Challenges to External Validity

Beyond the issue of the internal validity of alternate control studies, moreover, remained concerns regarding their applicability to the individual patient—their generalizability, or external validity—which again stalled the dissolution of serotherapy.[47] As mentioned in chapter 6, some attacks were limited to the particulars of serum administration used in Plummer's 1941 study, a foreshadowing of the persistent Achilles heel of controlled trials' susceptibility to agent-specific barbs.[48] Yet if Finland had served as the nexus for concerns regarding bias and confounding, Jesse Bullowa (ironically, given his onetime status as the champion of the controlled clinical trial) would offer the most persistent critique of the *generalizability* of the monotherapy-supporting alternate control pneumonia studies. And Bullowa would focus on the *patients* employed in the studies.

His evolving criticisms would harden in a time of increasing defensiveness re-

garding the utility of serotherapy as a supplement to the sulfonamides. In 1939 and 1940, however, Bullowa appears to have been motivated principally by his belief in the inability of clinical studies to adjudicate between monotherapy and combination therapy in the absence of appropriate clinical and laboratory stratification of the patients studied.[49]

In this respect, Bullowa's approach was paralleled by that of Arthur W. Frisch, a clinician working at the Detroit Receiving Hospital under the auspices of Michigan's Pneumonia Program and the Commonwealth Fund. As early as in the serotherapy-only days of early 1938, Frisch had hoped to stratify pneumonia patients into severity classes as determined by the ratio of free pneumococci to phagocytosed and agglutinated pneumococci in their sputum.[50] And by the 1939–40 winter pneumonia season, Frisch hoped ultimately to "individualize" pneumonia treatment and assign patients to one of four classes—supportive treatment, serum alone, sulfapyridine alone, or combination therapy—based on such findings.[51] By December of 1939, it was noted that, after initial house staff resistance to tailoring serum doses to degree of clinical severity, "individualizing" patient care was proceeding apace "as the regular staff learn[ed] that all patients do not require heavy doses."[52] Indeed, by the end of the pneumonia season, Frisch could recount: "The cases having an excellent prognosis received no serum or specific drug treatment of any kind and *all* recovered. Those having a good prognosis were given very small doses of serum and all recovered. Patients with a fair prognosis were treated with sulfapyridine, with a resulting fatality rate of 20 per cent, and those having the poorest prognosis of all were given both serum and sulfapyridine, with a resulting fatality rate of 28 per cent."[53] For Frisch, moreover, stratification could serve not only to individualize treatment but also to create "true" comparison groups for future controlled studies themselves:

> Most clinical trials of therapeutic agents in pneumonia have been based primarily on the method of alternate case selection. In order to obtain significant results large numbers of patients must necessarily be studied. The method fails to take into consideration those cases which would survive under any form of therapy and discards the overwhelmingly ill patients who expire shortly after admission to the hospital. The classification of cases into prognosis groups by means of sputum examination appears to be a method of case selection which would permit a true comparison of the efficacy of various therapeutic agents.[54]

In this reading, controlled studies *could* ideally become generalizable—once they had become more appropriately stratified.[55]

Bullowa, too, spoke at times along such lines. Indeed, his discriminatory lab-

oratory finding of choice as an indicator of those expected to benefit from combination therapy was the degree of free pneumococcal polysaccharide versus type-specific antibody in a patient's blood (not surprisingly, given his longstanding interest in the subject, as noted in chapter 2).[56] But Bullowa would himself generalize, arguing for finer and truer means of stratification broadly among the pneumonia alternate control studies:

> It has been well established that fewer patients succumb under chemotherapy and under serotherapy than without either of these. However, those patients recovering under one remedy may not be the same as would have recovered had they received that other possible treatment. Under certain conditions, one remedy may act more favorably than the other, so that there may be an appropriate remedy for each patient, as well as a better remedy for the majority. . . . It is the goal of therapeutic endeavor to set direct indications for remedies as well as to determine contraindications.[57]

As such, and echoing Finland's own evolving modus operandi regarding which subgroups of patients should receive monotherapy versus combination therapy, Bullowa offered a return to the nineteenth-century emphasis on the specific characteristics of patients themselves in determining treatment choices, a contrast to Cole's own triumphant emphasis on ever-finer microbiological specificity in directing such decisions.[58]

However, again as with Finland, further underpinning Bullowa's reliance on the laboratory—and linked to his longstanding emphasis on the laborious bedside generalship of the individual physician in waging war against the pneumococcus—was a further emphasis on the physician as strategist, as comfortable with pathophysiologic first principles as with the understanding and application of clinical studies.[59] Thus, at the very least, physicians could not be transformed on the basis of controlled trials into mere prescribing automatons, generalizing from limited trial data; with respect to the deadly pneumococcus, the choice of therapy could not "be left to rule of thumb."[60] The calculus of buffering the bloodstream of the patient with antibodies against the pneumococcus and its polysaccharides remained an active, dynamic task. Taken further, for those physicians (like Bullowa) who considered their own a priori pathophysiological knowledge to supercede the findings of what they considered poorly stratified controlled studies, legitimate room remained to ignore such trial data.[61] Seven months after Plummer's study was published, Bullowa would still recommend: "Because fatality rates of sulfapyridine-treated patients are greater when antibodies fail to appear, we believe it advisable to administer specific serum to those patients in

whom a failure of antibody formation is most likely to occur, i.e., those with infections caused by Pneumococcus type III, those with bacteremia or a positive reaction for capsular polysaccharide, those over 40 and those treated late in the course of their disease."[62]

Bullowa, in his defense of antipneumococcal antiserum, may have failed to recognize the slippery clinical slope to which he was leading. Six months after Bullowa's recommendation cited above, a West Virginia clinician, after clearly citing Plummer's study in an "Oration on Medicine" before the West Virginia State Medical Society, nonetheless admitted: "As nearly as I have been able to determine, the chief value of serum therapy in conjunction with the sulfonamides is in cases in which there is a type III infection, in which marked elevation of temperature persists beyond forty-eight hours [itself permitted by Plummer], and in which there are circulating capsular polysaccharides in the blood stream. In each instance the use of type-specific serum in a full dose is indicated. Some authorities believe that type-specific sera should be given to all patients over fifty years of age. My own personal preference is to make individual decisions in each case."[63] Indeed, such destabilizing approaches, when coupled with the minimal training most clinicians had in reading and interpreting clinical trials in the first place (and exacerbated by the profusion of sulfa drugs being introduced), could only contribute to the uncertainty faced by thoughtful clinicians at the time.[64]

Filling the Void: Pharmaceutical Interpretations

Instead, the void created could be filled to some extent by the certain voices of the pharmaceutical companies, playing their own critical roles in mediating the antipneumococcal therapeutic transition as they respectively championed their established and/or emerging products. As such, they would continue approaches begun decades earlier, while establishing their own novel precedents for the rapid and selective citing of both expert opinions and (ultimately) trial results themselves in buttressing their marketing efforts.[65] The respective efforts of Merck and Lederle merit particular mention.[66]

For Merck, the key was to present sulfapyridine as both revolutionary and relatively safe when used with care. As they claimed in the foreword to the 46-page sulfapyridine brochure (as mentioned in chapter 6) distributed to physicians by the end of 1939: "Among the changes in the methods of diagnosis and treatment of pneumococcic pneumonia that have taken place during a comparatively brief and recent time, there are two significant observations: First, the transition from the older classification, based chiefly on gross physical changes and their anatomic

distribution, to the more important etiologic classification; secondly, the impressive mortality reduction with the use of the new chemotherapeutic agent, Sulfapyridine."[67]

And in the course of eight pages of discussion of clinical studies attesting to sulfapyridine's efficacy—anchored by the very British studies that had been so abused by Bullowa, Plummer, and Finland in their joint 1939 *JAMA* article—Merck began by reporting on the "abundant confirmation" of the British studies by (predominantly American) researchers "from widely separated quarters."[68] They followed this with a thorough discussion of sulfapyridine's known toxicities, the specter of which, however, was frequently attenuated by the notion that such effects were either minor, rare, or to be largely avoided through "careful usage of the drug and close observation of the patient."[69]

Antiserum, it may be noted, was not mentioned by name in the above quote, but only implied by the nosological transformation of the "first" transition it had helped engender (and which, as will be discussed in chapter 8, was to be diluted by the nonspecific use of sulfapyridine and its descendants!). And pointedly, the mention that sulfapyridine had failed in two patients subsequently cured with serum by Long and Wood at Hopkins was overshadowed by the remark that in the same study, "the primary use of serum was discontinued and replaced by sulfapyridine, as the remarkable therapeutic efficacy of the drug became apparent."[70] Such was clearly to be the model for clinicians at large, with sulfa to supercede serum, itself relegated to backup. Indeed, at the end of the brochure, brief mention of the indications for combination therapy again focused on serum's backup role "if there is a failure of clinical improvement . . . within about forty-eight hours of adequate drug therapy, which includes the production and maintenance of an adequate blood concentration [of sulfapyridine]."[71] Sulfa prices vis-à-vis antiserum, in this context, did not need to be mentioned, but carried their own weight once sulfapyridine's efficacy and relative safety were established.

Merck's efforts did not go unrewarded. As pointed out by John Lesch, sulfapyridine contributed markedly to the company's growth in terms of the expansion of staff and equipment, research activity and publication rates, and—most prominently—sales figures.[72] As such, on the eve of World War II, sulfapyridine helped set the stage for Merck's still further antimicrobial-dependent expansion in the post–World War II era. And the promotion of sulfapyridine seems likewise to reside at an inflection point, on the eve of ever-greater pharmaceutical promotion in the era of clinical trial expansion itself.

Lederle—the largest producer of antipneumococcal antiserum in the country by the time of sulfapyridine's introduction—of course had a very different

agenda.[73] The company had not been caught as off guard by the advent of sulfapyridine as has been conventionally depicted.[74] Indeed, within a few years, American Cyanamid (of which Lederle had been a subsidiary since 1930) would apparently become the largest sulfa producer in the world.[75] Nevertheless, it certainly did have an investment in nearly thirty thousand rabbits and an entire system of antipneumococcal antiserum production and sales to protect;[76] and rather than immediately accept their destruction, Lederle continued to support the role of serotherapy in the wake of sulfapyridine's emergence. The company had established close ties in the serotherapeutic era with leading pneumonia experts (Bullowa and Finland, especially), and had long relied on them to test—and de facto, to promote—its expanding array of biologicals;[77] and in the first year after sulfapyridine's introduction, Lederle would rely on the opinions of its experts to support the continued use of serum.

Initially, in an anonymously authored article bearing many of Bullowa's fingerprints and published in its *Bulletin* prior to sulfapyridine's release for interstate sale, Lederle contrasted the established antipneumococcal antiserum with the novel sulfa drugs, minimizing the early British sulfapyridine studies while asserting: "Certainly the leading clinical investigators of the question have no thought now of turning from the thoroughly established principle of specific serum-therapy to chemo-therapy in pneumonia."[78] Further insisting that "there is, at the present time, no adequate experience in human beings for the efficacy of M&B 693 alone as a life-saving treatment for pneumococcic pneumonias," Lederle half-heartedly praised the sulfa drugs as potential "adjuvants" for serotherapy.[79] By April of 1939, however, again echoing Bullowa and Finland, and in conjunction with its own initial distribution of sulfapyridine, Lederle shifted to support for up-front combination therapy, declaring that "in the present preliminary state of our knowledge regarding the complementary action of these two agents, the physician who wishes to leave nothing to chance in his effort to save the life of his patient will not . . . postpone the administration of serum for two days, thus sacrificing the demonstrated advantage of an early administration of type-specific serum."[80] By October, again citing Bullowa, Plummer, and Finland in particular, Lederle would continue to emphasize both the synergistic activity of combination therapy and the reduction in sulfa toxicity afforded by the reduction in drug dosage subsequently required.[81]

By 1940, though, while attempting to stem the national retrenchment in serum usage, Lederle was forced to adhere at least to the restrictions in serum usage offered by Finland and Bullowa. The company would, however, continue to advocate combination therapy for generously chosen subgroups of patients (see

"YES SIR—They gave me serum too!"

Figure 5. By 1940, a year after the introduction of sulfapyridine, Lederle would continue to champion the use of antipneumococcal antiserum as a component of *combination* serochemotherapy. [Advertisement, personal collection of the author.]

fig. 5).[82] And by the eve of Plummer's study, Lederle could continue to note in advertisements that "combined serum and drug therapy is considered by many authorities as the optimum in pneumonia treatment today, and should be administered to all severely ill patients for whom the outlook is poor."[83] Even Plummer's study itself could be "spun" into serum advocacy for those patients unresponsive to the sulfa drugs alone within twenty-four to forty-eight hours.[84] But by the end of 1941 a number of factors—from Plummer's study itself, to the decline of the serotherapy-administering pneumonia control programs, to the dramatic shift in sales from serum to sulfa drugs by Lederle itself—appear to have led to an abandonment by Lederle of antipneumococcal serotherapy advertising and advocacy.[85] Serum's retrenchment would thus be both synergistically causative of, and affected by, Lederle's own withdrawal of support two years after the introduction of sulfapyridine.

Merck and Lederle, as such, had themselves helped to shape clinicians' readings of the perplexing array of antipneumococcal literature; and not only had they helped to shape the tempo and mode of the therapeutic transition from serum to sulfa, but they had also set a precedent, on the verge of the more widespread dissemination of statistical and clinical epidemiological thinking, for future pharmaceutical company "interpretation" of, and physician education concerning, evolving clinical studies. The post–World War II revolution in pharmaceutical marketing, as with the revolution in pharmaceuticals themselves (of which the sulfa drugs served as a leading edge), thus again appears more a revolution in scale than in kind.[86]

The Dismantling of Pneumonia as a Public Health Concern

The informational void that the pharmaceutical companies could fill with their rhetoric would be enlarged by the dismantling of pneumonia itself as a public health concern by the end of World War II. And as I relate in this chapter, many of the present dilemmas facing public health advocates with respect to respiratory tract infections—from antibiotic overprescribing to apparent pneumococcal polysaccharide vaccine underutilization—can be traced from their post–World War II origins. Such a process, finally, serves to epitomize the general impeachment of "therapeutic rationalism" as practiced, or the "republic of science" embodied, by autonomous practitioners in this era of the wonder drug.[1] Understanding its development offers windows into the limitations of the uses of specifics broadly as well as into the contested domains between private practice and public health themselves.

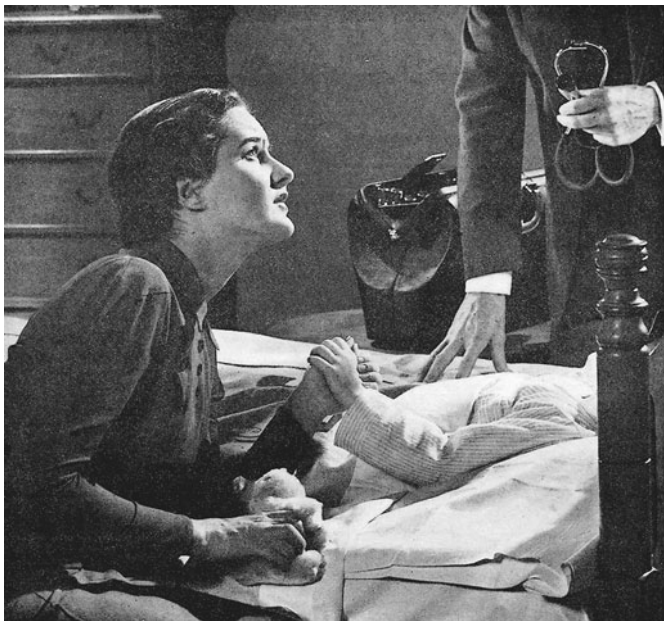
Pneumococcal "Transformation"—Again

To some extent, pneumonia's reversion to the domain of the private practitioner reflected the general fate of the public health system during World War II and its aftermath. During the war, as the United States experienced physician shortages nationwide due to enlistment in the armed forces, the pneumonia control programs themselves became depleted.[2] Furthermore, in the setting of virulent debate over the 1943 Wagner-Murray-Dingell bill and compulsory health insurance, the American Medical Association and its publicists more rigidly emphasized the primacy of the private practitioner vis-à-vis the government's representatives in the first place;[3] and over the ensuing decade, as attention increasingly focused on the wonders of scientific medicine, the means of its distribution became less of a national priority.[4]

But even within the public health system, pneumonia increasingly lost its standing as a priority after the advent of the inexpensive and widely accessible sulfonamides. Certain pneumonia control leaders would offer persistent claims that "to be more widely effective, the therapeutics of pneumonia, in the light of modern scientific knowledge, should be planned on a statewide basis . . . [such that] the lag between known medical science and its application be reduced to a minimum."[5] Yet in the eyes of the most important former pneumonia-control advocate—Surgeon General Thomas Parran himself—pneumonia would return to the domain of the individual practitioner over the course of the wartime experience. After rendering his final call for pneumonia control in April of 1940,[6] Parran increasingly focused on venereal disease and tuberculosis in particular as the nation's foremost public health concerns.[7] And with pneumonia apparently having "ceased to be a major menace" since the advent of the sulfa drugs,[8] Parran would, in 1944, exclude pneumonia from a list of disease entities meriting further dedicated research at his envisioned "national institutes for clinical research in . . . fields in which there is a large element of public interest."[9]

With such forces in motion, the pneumonia control programs themselves collapsed, with none apparently having survived the wartime effort.[10] Pneumonia reverted to a private disease, devoid of state oversight. As William Watt Graham Maclachlan, a prominent Pittsburgh pneumonia expert, would remark before Pennsylvania's state medical society three months after the society's own Edward Bortz had extolled the state's role in pneumonia control: "Now that the sulfonamides are being used so generously for, one might say, almost everyone who has pneumonia, the State's interest has been satisfied. What we do now, as individual physicians, is to study carefully the results of these drugs on our cases."[11] Tellingly, and not surprisingly, the novel concept introduced in 1940 by the Boston Dispensary to apply to the sulfonamide era the notion of a "pneumonia service"—a dedicated team of physicians or technicians to aid the private physician in the laboratory diagnosis and monitoring of the pneumonia patient—failed to attract adherents even in Massachusetts.[12]

In this setting, the failure of clinicians to "type" their lobar pneumonia cases became further emblematic of pneumonia's own transformation back into a private disease, increasingly managed with the use of less rigidly specific chemotherapeutics (or soon, antibiotics) alone. David Rutstein, prior to sulfapyridine's general release, had already feared that the general release of the drug would lead to a general reduction in pneumococcal typing.[13] And by 1941, even in Pennsylvania, which boasted perhaps the largest pneumonia control program in the country, clinicians failed to type nearly half the pneumonias reported to the state board



"Pneumonia!"

Figures 6–8. Within a little over a decade, pneumonia had been publicly transformed from a frightening emergency mandating immediate and collective attention to a neutered menace to be considered with complacency by individual practitioners. By the 1960s, however, certain clinicians would attempt to puncture such complacency itself. [Advertisements dating from 1937, 1945, and 1951, respectively; personal collection of the author.]

of health.[14] In certain military locales, where sulfa drugs could be administered "in tent hospitals, in small infirmaries in outlying posts or in field medical installations, even in the those that are necessarily without x-ray equipment or laboratory apparatus," typing likewise appeared an unnecessary luxury.[15] By late 1943, the title of a Nebraska clinician's presentation before the Omaha Mid-West Clinical Society neatly summarized the ethos: "In View of Present Day Treatment, Are Typing and Serums Necessary?"[16]

In this guise, much of the sense of urgency attached to the treatment of pneumonia was itself stripped away.[17] As early as 1940, Russell Cecil began publicly to lord it over his longstanding foe, noting smugly: "It would seem that the captaincy of the men of death is being passed on rather rapidly these days. I don't think pneumonia will rank as more than a sergeant in another year or so."[18] Soon a sense of complacency toward pneumonia was not only permitted but was even advocated in many presentations (cf. also figs. 6–8). Continuing the use of (by

We've come a long, long way in pneumonia

"I can remember the time when we fearfully awaited the 'crisis.' That was when pneumonia took about 125,000 lives every year. Since the use of 'sulfa' drugs which now conquer most of the 32 types of pneumococcus pneumonia, deaths have been reduced by 50%. And now with penicillin there will be even less. Notwithstanding, 500,000 people come down with pneumonia every year, and that's too many. Simple precautions that you can take will help make them fewer." *Your doctor*

TO HELP YOUR PHYSICIAN REMOVE PNEUMONIA AS A MAJOR HAZARD:

1. **Avoid fatigue and chilling**—If you are overtired, or if your resistance is low, watch out for pneumonia. Take care of common colds, sore throats, or grippe, as pneumonia often follows them.
2. **Call your doctor at once**—particularly if you have chills, fever, a cough, sharp chest pains, or if your sputum is discolored. Don't put off calling him because you think he is too busy.
3. **Follow his instructions faithfully**—The treatment prescribed by your doctor will help you get well. When you are over the acute phase of pneumonia, give yourself plenty of time for recovery. And while you are sick, don't expose others—remember, pneumonia is catching.

Upjohn

FINE PHARMACEUTICALS SINCE 1886

"Your Doctor Speaks"—This is the second of a series of messages sponsored by Upjohn to bring better health to more people through current medical knowledge

Thank heavens it's only pneumonia!

Pneumonia! . . . A hundred years ago, the word rang like a death knell for the very young and the very old! As recently as 1930, the mortality rate from pneumonia of children 5 to 9 years of age, under very favorable conditions, was about 20 per 100,000; whereas today, it is slightly over 2—a decline of 90 *per cent.* Fatality rates in adequately treated children have declined to minute proportions.

Public health measures, improved nutrition, increasingly available hospital facilities, and chemotherapy have all played their parts in this fortunate result. Sulfadiazine and penicillin dramatically controlled most pneumonias caused by microbes; but it remained for aureomycin to provide high effectiveness against both the *common pneumonias* caused by microorganisms and those of *unknown cause.*

Teamwork has provided the answer to the problem of pneumonia. Long and tedious researches, participated in by *Lederle*, resulted in effective serums for pneumonia. Subsequent researches by *Lederle* evolved sulfadiazine and aureomycin. These, integrated with increasing popular understanding of pneumonia, have essentially eliminated pneumonia as a major cause of death in this country. This teamwork between laboratory and clinical research workers, industry, and the public-at-large is typical of American preoccupation with working to do things *better*, for *more* people, by *everybody.*

Through research, they live who would have died!

Lederle

(Pronounced: Led'-er-lee)

A Division of American Cyanamid Company
30 Rockefeller Plaza, New York 20, N. Y.

this time nearly ubiquitous) military imagery to describe the "attack" on the demoted diplococcus,[19] a Virginia clinician declared by early 1942: "The reduction in the mortality of pneumonia is one of Medicine's greatest achievements. . . . A telling blow was dealt with serum therapy. Then came the blitzkrieg of the sulfonamides. Armed with these drugs, we can now regard pneumonia with a fair degree of complacency."[20]

In many instances, paralleling such a denigration of the pneumococcus was a denigration of the very antipneumococcal serotherapy that had once represented the only specific means to combat it, as the history of the treatment of pneumonia was again rewritten for fellow practitioners. Declared the Nebraska clinician cited above: "In 1927 we began to use serum for pneumonia patients, especially in the larger metropolitan areas. . . . Even then we were faced with the fact that many cases of pneumonia failed to respond to the antiserum. The antipneumococcus serum was heralded as a great advance in the treatment of pneumonia, but there were many disadvantages. . . . Also, statistically, nothing startling happened to the mortality figures from pneumonia during this period. . . . In 1937 we began to use the sulfa drugs for pneumonia. The results were spectacular."[21] The following month Norman Plummer, speaking before the New York Academy of Medicine, after again minimizing the contributions of serotherapy, would render such a transformation complete: "Lobar pneumonia, as it was known a comparatively few years ago, no longer exists today."[22]

"Specific" Concerns and the Limits of Rationalism

Concerns regarding such a reconfiguration were voiced from its inception by serotherapy's advocates, from early warnings that the widespread neglect of typing would preclude comparisons between serotherapy and chemotherapy, through those regarding typing's necessity for the application of combination therapy, to their final manifestation as pleas for up-front typing in preparation for those potential cases caused by sulfonamide-resistant organisms.[23] By early 1944 in New York City, where there had "recently been a large and increasing number of deaths from pneumonia . . . in spite of the availability of the sulfonamide drugs," the city's still-extant Pneumonia Advisory Committee bemoaned the absence not only of typing but even of bacterial diagnoses themselves, among pneumonia cases.[24] Noting that the reported pneumonia death rate was not only "particularly striking since it is occurring in an era when sulfonamide drugs are available . . . [but even] high in comparison with deaths in [*sic*] pneumonia reported in many of the years of the pre-sulfonamide era," the committee strove to

puncture the post-revolutionary smugness concerning the treatment of pneumonia.[25]

But such warnings were scarcely heeded. If anything, the merging of decreased reliance on bacterial diagnosis with reactions to pleas to continue to regard pneumonia with concern contributed to the extension of sulfa drug administration to upper respiratory tract infections as well by this time. As a Virginia practitioner, in a near-hysterical invocation of military analogy and with both a devaluation of physiology-based rationalism and a clear hit against centralized oversight, declared before his local medical society:

> And now I am starting in 1941 to use sulfathiazole and sulfapyridine prophylactically. And why not? It has not been proven to work that way! Not scientific, you say! Remember we are front line soldiers; when we see the enemy we do not have to wait for orders from headquarters through a long line of red tape. We must go for him, without waiting for the attack! Again, it seems to me, that is common sense medicine. What do we fear in grippe or a bad cold? Pneumonia. What do we fear in whooping cough and other contagious diseases, or post-operative? Pneumonia. If pneumonia develops, we have a remedy of proven value. Why wait? Can you tell when pneumonia is going to develop? If it does develop, you would use sulfathiazole or sulfapyridine with confidence. Then why not get the jump on those tough, little bacteria? Kill them before they get a foothold. Why wait for the attack? Bomb their channel ports! Wipe out their bases of supply! Prevent their starting out in the blood stream; meet force with force!"[26]

In more sober fashion, Plummer would declare in his above-cited New York Academy of Medicine presentation in November of 1943 (ironically, on the eve of one of New York's worst December pneumonia months ever): "Undoubtedly the most important reason today for the apparently low incidence of pneumonia is that many patients receive the sulfonamides in the very early stages of the disease, in some cases before the secondary infection following a cold has progressed to the stage of pneumonia, and the true nature of the infection is never known. This type of therapy is, of course, all to the good, and no longer can a physician be criticized for treating such a case without knowing the result of sputum typing and blood culture study."[27] Moreover, these tendencies would only be accentuated by the discovery of such "broad-spectrum" (i.e., capable of treating a wider realm of pathogens than could the sulfa drugs or penicillin) antibiotics as chloramphenicol and chlortetracycline by the late 1940s and early 1950s, as the entire ethos of specificity on which serotherapy had been built was being eroded.[28]

Again, a cadre of clinicians pleaded with their colleagues to avoid such in-

creasingly common—and potentially harmful—overextension. As early as 1939, the Mayo Clinic's H. Corwin Hinshaw had invoked a calculus of benefits and risks in assessing such activity: "For the most part, sulfapyridine should be used only for patients who are seriously ill. I doubt the advisability of using the drug for patients who have influenza, the common cold, sinusitis or tonsillitis. In such cases, this treatment may be worse than the disease, not only much more uncomfortable, but more dangerous."[29] Within four years, not only had the potential benefits of "prophylactic" therapy in upper respiratory tract infections failed to materialize,[30] but the potential for such practice patterns to lead to resistant organisms had become apparent to certain clinicians (including Russell Cecil and Norman Plummer themselves) as well.[31]

But the capacity of such clinicians to police or persuade their brethren with respect to the treatment of respiratory tract infections had been markedly curtailed by the end of World War II. And from the 1950s through the 1970s, such veterans of pneumonia control as Maxwell Finland and Harry Dowling would face an uphill battle in their self-conscious efforts to maintain "therapeutic rationalism" among their antimicrobial-prescribing contemporaries.[32] To be sure, Finland and Dowling would play important roles in fostering the next great round of FDA regulations—the Kefauver-Harris amendments of 1962, designed, among other things, to ensure drug efficacy (as opposed to safety alone) prior to drug marketing.[33] Nevertheless, they continued to encounter the same resistance to infringement on physicians' prescribing autonomy as they had faced in the setting of the pneumonia control programs. Finland, in particular, considered that, at the very least, "the complexity of modern medicine, the limitations of individual physicians, particularly those with large active practices, and the need for considerable amounts of detailed, well controlled and specialized studies, entirely preclude evaluation of important drugs by the 'play of the market place' or through 'tests by testimonials.'"[34]

But the American Medical Association had not only disbanded its Seal of Acceptance program (its strongest tool by which to influence the pharmaceutical industry and educate physicians) by 1955, but it opposed the passage of the Kefauver-Harris amendments themselves.[35] As the director of the AMA's legal and socioeconomic division wrote to Dowling two weeks after Finland's above-cited statement: "It is our belief that the determination of efficacy of a particular drug for a particular patient should be made by his physician and that the physician should have available to him those drugs which in his professional judgment he believes to be efficacious for his patient. This is basically the present situation and, as you know, it works out well. We do not think it would be wise to grant

efficacy evaluation powers to the government with the very foreseeable possibility that the government will usurp the physician's prerogative and decide for him which drugs he may have to use to treat his patients."[36] As such, despite the eventual passage of the Kefauver-Harris amendments, Finland, Dowling, and their colleagues recognized that the notion (and, to a large extent, the practice) of the unfettered, unmonitored clinician remained dominant.

Even their victories were limited. For instance, the two rationalists perhaps perceived the largest display of clinical irrationalism in the widespread use of the equally widely marketed "fixed-dose" combination antimicrobials (i.e., single pills made up of set doses of more than one active agent) so antithetical to their own expectations that clinicians would tailor therapy to the identified microbes and clinical context involved in any given infection. Yet as a fellow member of theirs on a federal panel of similar drugs reported to the FDA's commissioner at the time: "I do not believe that in the present instance we have been called upon to enter a debate on Federal Paternalism, Individual Freedom, Infringement of Private Enterprise, or on the Right of the Physician to Prescribe the Inefficacious (which I hold to be inalienable). Or have we?"[37] And despite the forced withdrawal by the late 1960s of most "fixed-dose" combination antimicrobials,[38] Finland, Dowling, and their colleagues were forced to realize that as with pneumonia control, education—instead of regulation—would more often have to suffice to ensure appropriate antibiotic prescribing.[39]

Paradigmatically, as applied to the rational approach to respiratory tract infections, they would have their work cut out for them. Already by the mid-1950s, a study of a community in South Dakota found that 92 percent of the population had received antibiotics during the preceding five years, over half of them for apparently inappropriate reasons.[40] Despite Ernest Jawetz's (of UCSF) plea—"Is it asking for too much that in a few areas [i.e., with respect to antibiotics] man behave as a rational being?"[41]—and the public attempts by Finland and his compatriots to attack such "omnibiotic" administration (as noted by James Whorton), Finland's fellow pneumonia-control veteran, Hobart Reimann, would lament by 1961 that "an estimated 90 per cent of the use of antimicrobics is unnecessary."[42] Over a decade later the situation would be reported as worse, if anything.[43]

From the 1950s through the 1970s, the self-styled rationalists' attention, with respect to the pneumococcus in particular, was drawn less to the potential for the selection of resistant strains than to the unwarranted adverse effects from such drugs. The pneumococcus had been considered "solidly ensconced as free of resistance, especially to penicillin G [which had superceded sulfadiazine as the drug of choice for lobar pneumonia by the late 1940s]."[44] Even Finland, commenting

in 1971 on the report of pneumococcal penicillin resistance found among both pneumonia patients and healthy carriers in New Guinea, considered that "the particular epidemiologic circumstances involved in the report . . . and the special properties of the strain of pneumococcus involved, make [the prospect of a more generalized increase in pneumococcal penicillin resistance] extremely remote."[45] And as scattered reports of pneumococcal penicillin resistance continued to emerge throughout the 1970s, with higher levels of resistance exhibited by particular strains by the end of the decade, Finland and his contemporaries would instead focus on the consequent need for the wider application of drug susceptibility testing in individual cases as well as the wider use of pneumococcal vaccination (itself dependent, ironically, on a return to typing to ensure the appropriate formulation).[46] The first soft requests for "limiting the injudicious use of antimicrobial agents" as a means to containing pneumococcal antimicrobial resistance would appear by the early 1980s,[47] but with pneumococcal penicillin resistance remaining at low levels throughout the decade (3.6% by 1987), concerns regarding the potential linkage between unfettered outpatient antibiotic overuse and the development of increasing antibiotic resistance likewise remained muted.[48]

By the early 1990s, however, the wider issue of antimicrobial resistance—among pathogens ranging from *Mycobacterium tuberculosis* to agents of nosocomial infection—would become a cause célèbre itself; and pneumococcal pneumonia would by this time serve to epitomize and even galvanize such broader clinical concerns.[49] Amid dire general warnings of an impending "crisis," and even of a "post-antimicrobial era,"[50] the early 1990s indeed witnessed a particular (if gradual) increase in pneumococcal resistance to penicillin and representatives of other antimicrobial classes. In this setting such increasing pneumococcal antibiotic resistance, perceived to have derived in large part from antibiotic overuse, would be cast not only as a stain on rational therapeutics but as a critical public health concern, mandating increased surveillance and reporting of such resistance on the one hand, and judicious avoidance of overprescribing for upper respiratory tract infections on the other.[51] As had been the case six decades earlier, "effective partnerships involving clinicians, public health officials, and patients" were called for, along with institutionally based "antibiotic control programs" themselves—almost the converse of their predecessor, specific-glorifying pneumonia control programs.[52] Yet both eras shared not only a call for greater physician education and oversight (rather than regulation), but for such education to be underpinned by pneumonia's transformation (or re-transformation) into a public health issue.[53]

The limits to this faith in the potential application of rational therapeutics, however, remain apparent. In a study of outpatient prescribing for the year 1992, over half of patients diagnosed with colds or upper respiratory tract infections (well known, by that time, to be unresponsive to antibiotics) were prescribed antibiotics;[54] when the same group analyzed national data from 1998, 55 percent of all antibiotic prescriptions rendered were still inappropriate.[55] By the same year, pneumococcal penicillin resistance had climbed to 24 percent among "invasive" disease isolates, with 14 percent of such isolates found to be multidrug-resistant.[56] Despite increasing attention by the Centers for Disease Control to the problem,[57] autonomous practitioners continued to contribute to the public health "emergency" through their inappropriate reliance on what had evolved into a decidedly nonspecific specific.[58] Perhaps no other issue has so vividly illustrated, for modern-day therapeutic rationalists, the ongoing limitations of the medical "republic of science."

The Fate of the Pneumovax

To some extent, such "irrationality" may have reflected the legacy of Jesse Bullowa's focus on the individual (as discussed in chapter 7) because sick patients in the office failed to appear before their physicians as representative types. Perhaps equally limiting to the application of rational therapeutics, however, was both an enduring faith in the specific (at the expense of concern with physiology-based rationalism and the mere treatment of symptoms) and a persisting resistance to including pneumonia within the domain of public health. Thus, clinicians not only resisted being told how to approach their patients but failed to concern themselves with the societal impact of antimicrobial prescribing as a whole. And as a final exemplar of the persisting limits to pneumonia's reconceptualization, this chapter concludes with a brief account of the history and present status of antipneumococcal vaccination.

Peter English, in his account of the inability of pneumococcal vaccination to take hold within the American medical profession in the first half of the twentieth century in particular, places critical emphasis on the ambiguity and limitations of the studies used to "prove" the vaccine's efficacy.[59] To extend his analysis, though, it seems that the fate of vaccine acceptance stemmed from an interplay among contemporary perceptions of the decisiveness of such studies, the relative availability and focus on the use of a specific to combat the infecting pneumococcus (likewise mentioned by English), and the relative degree to which pneumonia was conceptualized as a public health issue worthy of concerted "pre-

vention" in the first place. Moreover, such interplay would remain as relevant in the latter half of the twentieth century and beyond as it had in the first half.

Rufus Cole's evolving opinion of preventive pneumococcal vaccination reflects the evolution of the studies used to "prove" its efficacy in the first half of the twentieth century. After Sir Almroth Wright and F. Spencer Lister's initial attempts in the early 1910s at whole-pneumococcus vaccination in South African gold and diamond mines (densely populated with new, immunologically naive recruits from rural locations) had appeared suggestive, Cole had maintained a cautious optimism regarding similar studies among high-risk groups in America (e.g., geographically concentrated soldiers). He was, he said, "very anxious that the whole matter not receive a black eye in the beginning, as it may do if methods which are not the best are employed."[60] Yet while the pneumococcal vaccination studies performed by Russell Cecil among American army camps during World War I hardly delivered such a "black eye," the limitations to these studies (apparent in the difficult follow-up of patients in one study, and the confounding influence of the influenza epidemic, at the very least, in the other) certainly prevented Cole—or others, beyond Cecil himself—from lending their unqualified support to widespread use of the vaccine.[61]

More convinced of the utility of his therapeutic specific (despite, as described in chapter 1, its own failure to be "proved" efficacious through wartime studies), Cole thus gradually turned his attention away from preventive pneumococcal vaccination, setting the tone for the profession as a whole.[62] By the time of the national "pneumonia conference" convened in late 1937 (discussed in chapter 5), Surgeon General Parran essentially dismissed such vaccination, stating that the conference "must address itself to procedures that can be recommended for general application,"[63] an ethos echoed by critical fellow members of the very pneumonia vanguard attempting to transform the disease entity into a public health concern on the basis of therapeutic antiserum.[64]

By this time, however, such increasing public health concerns had partially restored a focus on prevention, augmented by the continuing contributions of applied immunology. In 1930 Thomas Francis and William Tillett at the Rockefeller had found that pure pneumococcal capsular polysaccharides, in the absence of a protein carrier, were immunogenic for humans.[65] Suggestive studies among Civilian Conservation Corps workers by Louis Dublin and his colleagues—using pneumococcal polysaccharide vaccines prepared by Lloyd Felton—continued to suffer from methodological limitations obvious to contemporaries,[66] but the advent of world war again afforded the concentration of young, healthy subjects for further study. By 1945, Rockefeller alumni Colin MacLeod and Michael Heidel-

berger could report, among more than eight thousand young men at the Army Air Force Technical School immunized with a polysaccharide vaccine against types I, II, V, and VII pneumococci, an 84 percent reduction in type-specific pneumonia cases as compared to non-immunized control patients (with no reduction realized against non-included types) over the course of seven months of follow-up.[67] Two years later, Paul Kaufman, in New York City, could lend complementary support through his controlled study of institutionalized elderly patients (mostly over the age of sixty) with a combined types I/II/III pneumococcal polysaccharide vaccine, revealing an apparently impressive reduction in both pneumonia incidence and overall mortality among the vaccinated over the course of up to six years of follow-up.[68]

For E. R. Squibb and Sons (who had partially supplied both MacLeod and Kaufman with the polysaccharide vaccine), declaring that "the [pneumonia] death rate is still far too high" while preparing the vaccine for the commercial market, such studies revealed that immunization was "obviously desirable on the widest possible scale."[69] MacLeod and Kaufman, however, had been more circumspect, arguing for vaccination chiefly among such high-risk groups as military recruits and the institutionalized (though Kaufman did suggest its use "generally in patients of old age").[70] But even such modest recommendations would be ignored in the wake of the advent of antibiotics and the collapse of pneumonia as a public health concern, forcing Squibb to take its vaccine off the market within four years of its introduction.[71] Two years after the Army Air Force study had appeared, a *Hygeia* article on "Pneumonia's Waterloo" reflected contemporary neglect of Macleod's achievement: "Perhaps the greatest achievements are represented by procedures such as vaccination against smallpox and diphtheria, that actually eliminates those diseases if carried out 100 percent. There is no known way to produce resistance to pneumonia. . . . That fact implies that medicine and pneumonia must meet always on a battlefield elected by the latter."[72] Warnings concerning the profession's persistent inability to save those patients in extremis upon hospital admission were occasionally voiced throughout the 1940s and 1950s,[73] but education regarding early treatment, rather than vaccination, was seen as the chief means of combating such remaining mortality.[74] In a 1963 article by Hobart Reimann on the "Prevention and Treatment of Pneumonias in the Older Person," vaccination did not garner a single mention.[75]

That same year, however, Robert Austrian and Jerome Gold reported a landmark study of 529 patients treated for pneumococcal bacteremia between 1952 and 1962 at the Kings County Hospital in Brooklyn.[76] They uncovered a mortality rate of nearly 25 percent among such patients, with 43 percent of the deaths

among those with pneumococcal pneumonia and bacteremia occurring within twenty-four hours of admission.[77] The mortality rate increased strikingly after the age of sixty, and over half the bacteremic cases were caused by pneumococci of seven capsular types.[78] Austrian and Gold considered it "questionable that a more effective antipneumococcal drug than penicillin can be developed," especially among those "having passed the physiologic 'point of no return' before . . . therapy was instituted."[79] Instead, they arrayed their findings behind a call for renewed focus on pneumococcal vaccination.[80] By the end of the decade, the federal government was listening, funding both the surveillance of prevalent pneumococcal types and further forays into vaccine development.[81]

In early 1969 a *Nature* editorialist optimistically noted that, after initial testing, "a polyvalent vaccine for mass-vaccination of high-risk groups should be ready by 1970";[82] but pneumococcal vaccination, over the ensuing three decades, would again face significant barriers to acceptance and dissemination. Once again, a complex interplay among the studies used to justify (or discredit) such vaccination, the fate of contemporary antipneumococcal specifics, and the perceived role of pneumonia as a public health concern would emerge, with strong parallels to that of the first half of the twentieth century.

Austrian, by then at the University of Pennsylvania, would collaborate with Merck to challenge the sufficiency of pneumococcal specifics and would become the leading advocate of vaccination throughout the remainder of the century.[83] Recapitulating the events of six decades prior, the first studies "proving" the efficacy of hexavalent, dodecavalent, and tridecavalent polysaccharide vaccines in preventing pneumococcal pneumonia were conducted among young South African mine workers;[84] and by late 1977, Merck's 14-valent Pneumovax had been licensed by the FDA and "recommended for the prevention of pneumococcal infection in high-risk patients."[85] Such "high-risk" groups, given traditional risk factors for pneumococcal sepsis, included the elderly and the immunodeficient, as well as those with such co-morbid illnesses as chronic obstructive pulmonary disease, congestive heart failure, cirrhosis, or diabetes mellitus. However, the legitimacy of generalizing from young, healthy subjects (with presumably more vigorous immune responses to vaccination) to members of such high-risk groups would soon be challenged,[86] and subsequent randomized controlled trials among high-risk group members in America published in the 1980s would be unconvincing.[87] While vaccine proponents could excuse such studies on account of insufficient sizes or through challenging the very endpoints chosen for analysis,[88] critics of the vaccine seem to have reflected (and further influenced) a gen-

erally low level of enthusiasm for administering the vaccine nationwide throughout the 1980s.[89]

For vaccine supporters, though, such studies revealed less about pneumococcal vaccination than about randomized controlled trials themselves, epitomizing an emerging recognition of the "limitations" of randomized controlled trials by the early 1980s.[90] In neo-Colean fashion, Austrian queried aloud as early as 1984 whether a definitive randomized controlled trial of pneumococcal vaccination would be ethically defensible (let alone fiscally or logistically possible) in view of the suggestive data accruing that attested to its efficacy.[91] Indeed, by the mid-1980s, studies using less glorified statistical means of "proving" vaccine efficacy—from case control to indirect cohort techniques—had suggested such efficacy in preventing pneumococcal bacteremia in particular,[92] leading one vaccine proponent to conclude: "In many areas of clinical medicine, a well-founded biologic rationale, together with favorable experience under less than fully controlled circumstances, justifies a decision to treat."[93]

But what appears to have led to increasing rates of pneumococcal vaccination in the following decade was less the convincing nature of such arguments than—as the converse of yet another situation from half a century prior—the perceived emerging *failure* of antipneumococcal specifics in the wake of increasing pneumococcal resistance. The specter of pneumococcal penicillin resistance had been raised since its emergence by pneumococcal vaccine supporters to justify more widespread vaccination;[94] however, vaccination rates did not truly escalate until the period from 1991 to 1996, the same time period during which pneumococcal resistance achieved widespread notoriety.[95] By the end of the decade, Robert Breiman of the Centers for Disease Control could optimistically cite such an influence as fomenting "a new romance" with preventive vaccination among clinicians whose "love affair with therapeutics" had begun to wilt.[96]

Such a romance, however, would fail to fully bloom. For one thing, the absence of a definitive randomized controlled trial justifying the application of pneumococcal vaccination to such high-risk groups as those aged sixty-five and older would remain unsettling, continuing to polarize clinicians into those who regarded such a process as impugning pneumococcal vaccination, versus those who denied the necessity of a randomized controlled trial itself to justify widespread vaccination in the wake of the emergence of still more suggestive indirect studies.[97] Moreover, the absence of a convincing, widely generalizable randomized controlled trial has appeared perhaps still more unnerving in the context of the recent impeachment of less direct studies vis-à-vis randomized controlled tri-

als in such a high-profile case as that regarding the benefits of hormone replacement therapy in preventing cardiovascular disease in women.[98]

But despite the absence of a study as clear-cut as has been recently used to confirm the utility of a protein-polysaccharide conjugate vaccine for the prevention of pneumococcal disease in young children,[99] the pneumococcal polysaccharide vaccine *has* been considered relatively efficacious (and cost-effective) in the prevention of pneumococcal bacteremia in adults by most clinicians polled and by voices of considerable authority among the medical profession.[100] Rather, perhaps the American medical profession's inability to reconceptualize pneumonia as a public health concern has continued to render pneumococcal vaccine administration a low priority. Since 1979 vaccine supporters have lamented the "information gap" among both clinicians and their patients, precluding more widespread application of the vaccine.[101] Remedies ranging from patient-focused to physician-focused have been proposed, and attempts to have the vaccine administered in such non-office settings as upon discharge of high-risk patients from hospitals have been implemented in certain locations, but only partial gains have been reported to date.[102] By 2001, national vaccination rates of those sixty-five and older remained at approximately 60 percent, far below the national objective to have greater than 90 percent of this population immunized by the year 2010.[103]

Instead, it appears that if the gains afforded by pneumococcal vaccination are considered real but relatively modest (and unable to be measured) at the individual level, then given the persisting "ownership" of the disease by antibiotic-wielding private practitioners today, federal efforts to reconceptualize pneumonia as a public health concern will once again be a necessary prerequisite to continued gains in adult pneumococcal vaccination studies and rates (and to a parallel reduction in antibiotic overuse).[104] An understanding of the contingent nature of pneumonia's changing status as a public health concern throughout the twentieth century demonstrates the potential fluidity of the boundary between private practice and public health and the feasibility of pneumonia's re-transformation into such a public health concern. At the same time, an appreciation of the history of such efforts underscores the degree to which a partnership among private practitioners, public health advocates, and the lay public will be necessary to ensure the success of such a transformation.

Overcoming Resistance

Throughout this book, I have attempted to use the evolving treatment of pneumonia as a lens through which to examine the changing "therapeutic perspective" of twentieth-century American medicine. Several key themes have emerged: the profession's increasing focus on the use of the specific; the changing means of gauging therapeutic efficacy and influencing therapeutic application; the evolving domains between public health and private practice in controlling and combating disease; and the manner and consequences not only of general therapeutic change, but of the profession's own ongoing therapeutic self-identification. Focusing on the treatment of a particular disease such as pneumonia has revealed that while at times the changing approach to its treatment reflects general trends, at times it appears to serve as a model and to drive such general trends themselves. In other words, formal aspects of broad therapeutic application or evaluation are sometimes nearly as much at stake in a given instance of therapeutic evolution as any localized, content-driven aspect of the event, and focusing on a particular disease entity accentuates and clarifies the interplay among such therapeutic "form" and "content" over time.[1]

More "specifically," a key theme of the book has been my attempt to draw attention to a relatively forgotten era of therapeutics in American medicine: the period between the Golden Age of Microbiology and the Antibiotic Revolution, particularly as exemplified by antimicrobial efforts. Rather than representing a barren era in anticipation of some unknown transformation to come, the efforts of the first four decades of twentieth-century American medicine—for better or worse—in many ways shaped the use of, and reliance on, the specific throughout the twentieth century and beyond. Approaches throughout the era to the pneumococcus—a fundamental source of biological and therapeutic inquiry to a degree mutually and dramatically lessened in the post–World War II era[2]—embodied the tempo and mode of a critical therapeutic transformation in American medicine at the crossroads of biologicals and biometrics.

Kenneth Ludmerer has focused on the degree to which radical changes with respect to medical education and research in the interwar era set the stage for still greater changes after World War II; to only a slightly lesser degree, the same holds true with respect to therapeutics.[3] From an evolving intertwining between fundamental science and the clinic, to an increasing reliance on the therapeutic specific at the expense of attention to physiology-based rationalism, a changing standard of therapeutic efficacy, and an enlarging role of the pharmaceutical industry in attaching itself to and fostering such changes, the foundations for the respective post–World War II "revolutions" in bioscience/clinical interaction,[4] therapeutics (embodied by the advent of antibiotics),[5] clinical epidemiology,[6] and pharmaceutical marketing[7] had been set in place over the previous half-century.

What becomes striking is the degree to which this era in therapeutics has subsequently been submerged, and what this process reveals about the profession's own ongoing self-identification. A tension has long existed between the American medical profession's inherent therapeutic conservatism and its progressivistic, positivistic rhetoric.[8] And such rhetoric still belies an ongoing therapeutic irrationalism characterized by heterogeneity in practice patterns,[9] the large-scale failure to apply the "evidence-based medicine" to which the profession purports to aspire,[10] and the ongoing influencing of such practice patterns by pharmaceutical marketing efforts.[11]

None of this is surprising; indeed, it has been my intention to demonstrate that much of this carries deep historical roots. Given the apparent limits to the application of clinical epidemiological findings in all their former and present guises (from the advent of biometrics to the seeming triumph of the blinded randomized control trial), an ongoing resistance by autonomous practitioners to the encroachment of such universal clinical epidemiological science on the art of therapeutic management has characterized American medicine for over a century. In constructing artificial boundaries between its past and present, the profession thus forgoes the opportunity to appreciate the origins and depth of such resistance to the application of "therapeutic rationalism" in its present manifestations.[12]

Finally, and closely related, such artificial boundaries likewise exist in another key aspect of the American medical landscape, namely, in demarcating the domain between private practice and public health. In the 1930s, the reduction of mortality from pneumonia was reconstructed as a community problem, necessarily entailing the input of public health departments and physician assistance and re-education. The ephemeral nature of pneumonia's configuration as a public health concern reveals how contingent such domain allocations may be. But

given contemporary concerns ranging from increasing antibiotic resistance to apparently insufficient vaccination rates, there appears to be no reason that specific-wielding practitioners of today should resist the input—and even the encroachment—of public health authorities in combating, at the community level, the ever-present Captain of the Men of Death. And if ongoing ignorance and lost opportunities should be considered the true Captains of the Men of Death today, then efforts to overcome these maladies remain central to enriching the therapeutic perspective of American medicine in the twenty-first century and beyond.

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Abbreviations

ANRP	Alfred Newton Richards Papers, University of Pennsylvania
BHR	Bellevue Hospital Records
CWP	C. E. A. Winslow Papers, Yale University
FBP	Francis Blake Papers, Yale University
HDP	Harry Dowling Papers, National Library of Medicine
LDP	Louis Dublin Papers, National Library of Medicine
LFP	Lee Frankel Papers, American Jewish Historical Society
LLP	Lucius Littauer Papers, Harvard University Archives
MA	Merck Archives, Whitehouse Station
MFP	Maxwell Finland Papers, Countway Medical Library
MLIC	Metropolitan Life Insurance Company Archives
NDA	Sulfapyridine New Drug Application, FDA Records, Rockville, Maryland
RAC	Commonwealth Fund Records, Rockefeller Archive Center
RCP	Rufus Cole Papers, American Philosophical Society
RG90	Public Health Service Records, National Archives
RG112	Records of the Office of the Surgeon General (Army), National Archives
RG443	National Institutes of Health Records, National Archives
TPP	Thomas Parran Jr. Papers, University of Pittsburgh Archives Service Center
WMP	William S. Middleton Papers, National Library of Medicine
YU	Yale University (Medical School Theses)

Introduction

1. For the nearly tragic and almost farcical manner in which the patient was seemingly overtreated by the Rockefeller Institute's emissaries (as viewed by the Boston City Hospital's representatives), see Maxwell Finland, *The Harvard Medical Unit at Boston City Hospi-*

tal, Vol. I (Boston: Commonwealth Fund Publication, 1982), 325–26; Maxwell Finland and William B. Castle, eds., *The Harvard Medical Unit at Boston City Hospital,* Vol. II, Part 1 (Boston: Commonwealth Fund Publication, 1983), 271–72.

2. "The Pneumonia Film, 'A New Day,'" *Journal of the American Medical Association* 110 (1938): 514.

3. *A New Day in Health Protection,* 2–5 [MLIC, Box 160605]; *Press Book: A New Day* [MLIC, Box 160605]; "Teaching Health with Metropolitan Films," *Metropolitan Underwriter* 13 (1943): 15.

4. American Council on Education, *Selected Educational Motion Pictures, a Descriptive Encyclopedia* (Washington, D.C.: American Council on Education, 1942), 207–8.

5. For an introduction to the evolution and impact of such twentieth-century "specifics," see Edmund D. Pellegrino, "The Sociocultural Impact of Twentieth-Century Therapeutics," in *The Therapeutic Revolution: Essays in the Social History of American Medicine,* ed. Morris J. Vogel and Charles E. Rosenberg (Philadelphia: University of Pennsylvania Press, 1979), 245–66.

6. See Warwick Anderson, Myles Jackson, and Barbara Gutmann Rosenkrantz, "Toward an Unnatural History of Immunology," *Journal of the History of Biology* 27 (1994): 582; see also, Hans-Jörg Rheinberger, *Toward a History of Epistemic Things: Synthesizing Proteins in the Test Tube* (Stanford, Calif.: Stanford University Press, 1997).

7. Charles E. Rosenberg, "The Therapeutic Revolution: Medicine, Meaning, and Social Change in Nineteenth-Century America," in *The Therapeutic Revolution,* ed. Vogel and Rosenberg, 3.

8. John Harley Warner, *The Therapeutic Perspective: Medical Practice, Knowledge, and Identity in America, 1820–1885* (Cambridge, Mass.: Harvard University Press, 1986).

9. For a discussion of the persistence of "therapeutic enthusiasm and the pharmacological 'imperative'" in the twentieth century, see Pellegrino, "The Sociocultural Impact of Twentieth-Century Therapeutics," 258.

10. See, e.g., Charles E. Rosenberg, *The Care of Strangers: The Rise of America's Hospital System* (New York: Basic Books, Inc., 1986), 142–65; Rosemary Stevens, *In Sickness and in Wealth: American Hospitals in the Twentieth Century* (New York: Basic Books, 1989), 52–79; Joel D. Howell, *Technology in the Hospital: Transforming Patient Care in the Early Twentieth Century* (Baltimore: Johns Hopkins University Press, 1995); Keith Wailoo, *Drawing Blood: Technology and Disease Identity in Twentieth-Century America* (Baltimore: Johns Hopkins University Press, 1997).

11. For the farthest-reaching exception, written by a participant scientist, see Harry F. Dowling, *Fighting Infection: Conquests of the Twentieth Century* (Cambridge, Mass.: Harvard University Press, 1977).

12. See, e.g., Nancy Tomes, *The Gospel of Germs: Men, Women, and the Microbe in American Life* (Cambridge, Mass.: Harvard University Press, 1998), 6; Gerald N. Grob, *The Deadly Truth: A History of Disease in America* (Cambridge, Mass.: Harvard University Press, 2002), 201.

13. For rare representatives, see Harry F. Dowling, "Frustration and Foundation: Management of Pneumonia before Antibiotics," *Journal of the American Medical Association* 220 (1972): 1341–45; idem, "The Rise and Fall of Pneumonia-Control Programs," *Journal of In-*

fectious Diseases 127 (1973): 201–6; Michael Worboys, "Treatments for Pneumonia in Britain, 1910–1940," in *Medicine and Change: Historical and Sociological Studies of Medical Innovation,* ed. Ilana Löwy (London: John Libbey and Company, Ltd., 1993), 317–35; Harry M. Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (New York: Cambridge University Press, 1997), 60–67.

14. John Bunyan had first referred to consumption in 1680 as "the captain of all these men of death" in *The Life and Death of Mr. Badman.* By the turn of the twentieth century, in the fourth edition of his *Principles and Practice of Medicine,* Osler had famously transferred the title to pneumonia. See Bunyan, *The Life and Death of Mr. Badman and the Holy War,* ed. John Brown (Cambridge: Cambridge University Press, 1905), 157; William Osler, *Principles and Practice of Medicine,* 4th ed. (New York: D. Appleton and Co., 1901), 108.

15. For an early equation of pneumonia with a Grendel-like "Monster," see Edwin Ward Finch, *The Frontier, Army and Professional Life of Edwin W. Finch, M.D., with Suggestive Thoughts from his Own Personal Experiences in the Treatment of Pneumonia, Etc.* (New Rochelle: Simmons, Manning, and Dawson, 1909), 66. Military metaphors would be repeatedly used to describe the therapeutic approach to pneumonia throughout the era described in this book, epitomizing the application of military metaphors to therapeutics broadly throughout the twentieth century. For the rise of such broad application, see S. L. Montgomery, "Codes and Combat in Medical Discourse," *Science as Culture* 2 (1991): 366–67; for its persistence as applied to the pneumococcus, see Morton N. Swartz, "Attacking the Pneumococcus—A Hundred Years' War," *New England Journal of Medicine* 346 (2002): 722.

16. "Its treatment has varied with every period in the development of medicine. The history of the treatment of penumonia [*sic*] is a rare chapter because in a narrow sense it is a history of therapeutics" (Stewart R. Roberts, "The Treatment of Pneumonia," *Journal of the Medical Association of Georgia* 14 [1925]: 113).

17. William Osler, *The Principles and Practice of Medicine* (New York: D. Appleton, 1892), 529.

18. See Martin S. Pernick, *A Calculus of Suffering: Pain, Professionalism, and Anesthesia in Nineteenth-Century America* (New York: Columbia University Press, 1985).

19. See, for example, Merle A. Sande, "'Wonder Drug' Misuse, Abuse," *Internal Medicine News* 32 (1999): 17.

20. See, for example, Allan M. Brandt, *No Magic Bullet: A Social History of Venereal Disease in the United States since 1880* (New York: Oxford University Press, 1985), 4–5.

21. Ironically, Paul Ehrlich had initially coined the term "magic bullet" to describe the activity of therapeutic antibodies, with chemotherapy considered only to aspire to such precision. See Martha Marquart, *Paul Ehrlich* (New York: Henry Schuman, 1951), 91; Paul Ehrlich, "Chemotherapy," in *The Collected Papers of Paul Ehrlich, Volume III, Chemotherapy,* ed. F. Himmelweit (New York: Pergamon Press, 1960), 510.

22. Regarding the medical "republic of science," see Marks, *Progress of Experiment,* 4–5, 231–38.

23. Operationally, I have limited my scope of inquiry to the treatment of pneumonia in adults because antipneumococcal serotherapy was infrequently used for children, given their low case fatality rate on the one hand, and such difficulties as obtaining sputum and

inserting intravenous catheters on the other. See Roderick Heffron, *Pneumonia: With Special Reference to Pneumococcus Lobar Pneumonia* (New York: Commonwealth Fund, 1939), 834–35.

PART I. SEROTHERAPY AND THE RISE OF THE SPECIFIC, 1891–1930

1. Octavius Sturges and Sidney Coupland, *The Natural History and Relations of Pneumonia: Its Causes, Forms, and Treatment: A Clinical Study* (London: Smith, Elder, and Company, 1890), 1. While Sturges and Coupland practiced in London, their declaration could easily have been made at the time by practitioners across the Atlantic.

2. As an introduction to the history of pneumonia over the past two millennia, see Edward P. Wells, "An Introduction to the Study of Pneumonic Fever," *Journal of the American Medical Association* 12 (1889): 187–90; Campbell P. Howard, *The Diagnosis and Treatment of Pneumonia* (New York: Oxford University Press, 1936), 4–6.

3. Ibid., 2–3.

4. Compare, for example, George B. Wood, *A Treatise on the Practice of Medicine* (Philadelphia: Grigg, Elliot, and Company, 1847), 2:43–46; Austin Flint, A. Clark, John T. Metcalfe, and Benjamin W. M'Cready, *Report of a Committee of the Associate Members of the Sanitary Commission on the Subject of Pneumonia* (New York: Baker and Godwin, Printers, 1862). For American revisions of contemporary British textbooks, compare George Gregory, *Treatise on the Theory and Practice of Physic, with Notes and Additions, Adapted to the Practice of the United States,* ed. Nathaniel Popper and S. Calhoun (Philadelphia: Towar and Hogan, 1826), 377–83; Thomas Watson, *Lectures on the Principles and Practice of Physic Delivered at Kings College, London, 2nd American Revision, with Additions,* ed. D. Francis Condie (Philadelphia: Lea and Blanchard, 1845), 584–87; William Aitken, *The Science and Practice of Medicine, From the 4th London Edition, with Additions,* ed. Meredith Clymer (Philadelphia: Lindsay and Blakiston, 1866), 2:741–749. See also Donald A. Dukelow, "Pneumonia Then and Now," *Today's Health* 34 (1956): 42–43. Regarding the broad changes in "therapeutic perspective" in America throughout the era, see John Harley Warner, *The Therapeutic Perspective: Medical Practice, Knowledge, and Identity in America, 1820–1885* (Cambridge, Mass.: Harvard University Press, 1986), 91–102.

5. For a history of the independent discovery of the pneumococcus by Louis Pasteur and George Sternberg, see Benjamin White, *The Biology of the Pneumococcus: The Bacteriological, Biochemical, and Immunological Characters and Activities of Diplococcus Pneumoniae* (New York: Commonwealth Fund, 1938), 2–21. Regarding the ensuing debate concerning the roles of the pneumococcus and Friedländer's bacillus as agents of pneumonia, see Robert Austrian, "The Gram Stain and the Etiology of Lobar Pneumonia: An Historical Note," in *Life with the Pneumococcus: Notes from the Bedside, Laboratory, and Library* (Philadelphia: University of Pennsylvania Press, 1985), 5–13.

6. See E. Metchnikoff, "Ueber eine Sprosspilzkrankheit der Daphnien. Beitrag zur Lehre über den Kampf der Phagocyten gegan Krankheitserreger," *Archiv für pathologische Anatomie und Physiologie und für klinische Medicin* 96 (1884): 177–95; reprinted in Debra Jan Bibel, *Milestones in Immunology: A Historical Exploration* (Madison, Wis.: Science Tech Publications, 1988), 121–24. For the fullest exposition of Metchnikoff's evolving theory of

cellular immunology, see Alfred I. Tauber and Leon Chernyak, *Metchnikoff and the Origins of Immunology: From Metaphor to Theory* (New York: Oxford University Press, 1991).

7. George H. F. Nuttall, "Experimente über die bacterienfeindlichen Einflüsse des thierischen Körpers," *Zeitschrift für Hygiene und Infektionskrankheiten* 4 (1888): 353–94; reprinted in Bibel, *Milestones in Immunology,* 163–66. Regarding the immediate initiation of a struggle between supporters of cellular versus humoral immunity (to be dominated during its first half-century by the humoralists), see Arthur M. Silverstein, *A History of Immunology* (San Diego, Calif.: Academic Press, Inc., 1989), 49–56; Tauber and Chernyak, *Metchnikoff and the Origins of Immunology,* 149–74.

8. E. Behring and S. Kitasato, "Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thierren," *Deutsche Medizinische Wochenschrift* 16 (1890): 1113–14; reprinted in Bibel, *Milestones in Immunology,* 12–15.

9. G. Klemperer and F. Klemperer, "Versuche über Immunisirung und Heilung bei der Pneumokokkeninfection," *Berliner Klinische Wochenschrift* 28 (1891): 833–35; as discussed in Edwin A. Locke, "The Serological Treatment of Lobar Pneumonia," *Boston Medical and Surgical Journal* 190 (1924): 197.

10. See, e.g., Arthur M. Silverstein, "The Dynamics of Conceptual Change in Twentieth Century Immunology," *Cellular Immunology* 132 (1991): 521.

11. Indeed, many of the salient aspects of the history of antipneumococcal serotherapy—from the ongoing nosological evolution serotherapy engendered to the tensions created between private physicians and public health departments in its implementation—applied to that of diphtheria antitoxin as well, as told in Evelynn Maxine Hammonds' *Childhood's Deadly Scourge: The Campaign to Control Diphtheria in New York City, 1880–1930* (Baltimore: Johns Hopkins University Press, 1999).

Chapter 1. The Advent of Type-Specific Antipneumococcal Serotherapy

1. J. W. Washbourn, "Antipneumococcic Serum," *British Medical Journal* (1897): 1849. See also Nicola Pane, "Ueber die Heilkraft des aus verschiedenen immuisierten Tieren gewonnenen antipneumonischen Serums," *Zentralblatt für Bakteriologie, Parasitenkunde u. Infektionskrankheiten* 21 (1897): 664–74; as discussed in Edwin A. Locke, "The Serological Treatment of Lobar Pneumonia," *Boston Medical and Surgical Journal* 190 (1924): 197.

2. Joseph Eichberg, "The Serum Treatment of Pneumonia," *American Medicine* 3 (1902): 692.

3. Bruce W. Goldsborough, "A Contribution to the Treatment of Pneumonia with Antipneumococcic Serum," *Journal of the American Medical Association* 38 (1902): 1681.

4. Eichberg, "The Serum Treatment of Pneumonia," 692.

5. J. M. Anders, "Serum Treatment of Pneumonia," *Journal of the American Medical Association* 43 (1902): 1780.

6. As late as 1914, William Williams, using antipneumococcal antiserum provided by the same New York Department of Health made famous through its provision of diphtheria antitoxin, reported disappointing results among patients treated at New York Hospital. See William R. Williams, "Twenty-Three Cases of Pneumonia Treated with Antipneumococcus Serum," *Archives of Internal Medicine* 13 (1914): 978–86. A Chicago clinician would

concur a year later: "The various specific sera never yielded favorable results and in recent years have been very little used" (Joseph L. Miller, "Value of Specific Treatment in Croupous Pneumonia," *Illinois Medical Journal* 28 [1915]: 409).

7. F. Neufeld and L. Händel, "Ueber Herstellung und Prüfung von Antipneumokokkenserum und über die Aussichten einer spezifischen Behandlung der Pneumonie," *Zeitschrift für Immunitätsforschung und experimentelle Therapie* 3 (1909): 159–71; F. Neufeld and L. Händel, "Über die Entstehung der Krisis bei der Pneumonie und über die Wirkung des Pneumokokkenimmunserums," *Arbeiten aus dem Kaiserlichen Gesundheitsamte* 34 (1910): 166–81; idem, "Weitere Untersuchungen über Pneumokokken-Heilsera," *Arbeiten aus dem Kaiserlichen Gesundheitsamte* 34 (1910): 293–304; idem, "Zur Frage der Serumtherapie der Pneumonie und der Wertbestimmung des Pneumokokkenserums," *Berliner Klinische Wochenschrift* 49 (1912): 680–83; as discussed in Locke, "The Serologic Treatment of Lobar Pneumonia," 197. Neufeld also made the first attempt on a handful of pneumonia patients at what would come to be known as "type-specific" serotherapy.

8. Rufus Cole, "The Opening of the New Hospital of the Rockefeller Institute" [RCP, filed under "Cole, RI, Notes for Articles"]. See also A. McGehee Harvey, *Science at the Bedside: Clinical Research in American Medicine, 1905–1945* (Baltimore: Johns Hopkins University Press, 1981), 78–89.

9. Rufus Cole to F. Neufeld, 4/22/10; F. Neufeld to Rufus Cole, 4/3/12 [both in RCP].

10. Cole, "The Opening of the New Hospital of the Rockefeller Institute" [RCP].

11. A. R. Dochez and L. J. Gillespie, "A Biologic Classification of Pneumococci by Means of Immunity Reactions," *Journal of the American Medical Association* 61 (1913): 727–30. In South Africa, working under Almroth Wright, F. Spencer Lister had almost simultaneously noted the serological differentiation of pneumococci into such groupings. He would reference the Rockefeller findings as a postscript to his own publication. See F. S. Lister, "Specific Serological Reactions with Pneumococci from Different Sources," *Publications of the South African Institute for Medical Research* 1 (1913): 1–14. Regarding the contemporary South African pneumococcal research in general, see Robert Austrian, "Of Gold and Pneumococci: A History of Pneumococcal Vaccines in South Africa," *Transactions of the American Clinical and Climatological Association* 89 (1977): 141–61.

12. Rufus Cole, "Treatment of Pneumonia by Means of Specific Serums," *Journal of the American Medical Association* 61 (1913): 664.

13. For a broad history of the debates concerning immunological specificity during the first decades after the emergence of immunology as a field, see Pauline M. H. Mazumdar, *Species and Specificity: An Interpretation of the History of Immunology* (New York: Cambridge University Press, 1995).

14. Indeed, formerly deemed harmless, the potentially "pro-infective action of normal foreign serum" was now noted by Cole. See Rufus Cole and A. R. Dochez, "Report of Studies on Pneumonia," *Transactions of the Association of American Physicians* 28 (1913): 612.

15. Cole, "Treatment of Pneumonia by Means of Specific Serums," 665. In his presentation, Cole explicitly omitted from the series two patients "admitted in the last stages of the disease and [to whom the serum was] . . . administered only a few hours before the patients died." The very first patient treated by Cole, who recovered, had been treated in Jan-

uary of 1913. See "Rockefeller Institute Hospital Pneumonia Cases Serum Treated and Untreated, 1910–1929" [RCP].

16. Cole and Dochez, "Report of Studies on Pneumonia," 612.

17. Rufus Cole to F. Neufeld, 5/1/14 [RCP].

18. Regarding Cole's initial reluctance to send out serum (on account of limited supplies of serum and fears of damning the therapy by permitting its use in less intensive settings), see Rufus Cole to Alfred MacConley, 1/14/14; Rufus Cole to James Jobling, 3/10/15 [both in RCP]. There is a certain irony to Cole's reluctance to share with Jobling, given that Simon Flexner and Jobling, in the decade prior, had required the help of numerous clinicians at outside institutions to test the efficacy of their "anti-meningitis" serum. See Simon Flexner and J. W. Jobling, "An Analysis of Four Hundred Cases of Epidemic Meningitis Treated with the Anti-Meningitis Serum," *Journal of Experimental Medicine* 10 (1908): 690–733. Cole, working with an endemic disease and with a hospital at his disposal, was less desperate. The Rockefeller's eventual grateful recipients of type I antipneumococcal serotherapy included Henry Chickering at UCSF (who would himself send samples to a colleague in Honolulu!), Henry Christian at Brigham and Women's Hospital in Boston, and Pittsburgh's Lawrence Litchfield (who would remark to Cole: "The profession out here are beginning to sit up and take notice, and I have increasing demands for the serum for bona fide type I cases"). See Henry Chickering to Rufus Cole, 9/27/15; Rufus Cole to Henry Christian, 12/11/16; and Lawrence Litchfield to Rufus Cole, 3/9/17 [all in RCP].

19. Francis Blake to Rufus Cole, 12/18/17 [RCP].

20. G. B. Stanistreet to Simon Flexner, 4/8/15 [RCP, filed under "Flexner, Simon"].

21. Henry J. Nichols, "The Lobar Pneumonia Problem in the Army from the Viewpoint of the Recent Differentiation of Types of Pneumococci," *Military Surgeon* 41 (1917): 154. The selection basis of such treatment differences was not reported.

22. Ibid., 155.

23. Oswald T. Avery, H. T. Chickering, Rufus Cole, and A. R. Dochez, *Acute Lobar Pneumonia: Prevention and Serum Treatment* (New York: Rockefeller Institute for Medical Research, 1917), 4, 5. Cole was also quick to note the potential of mobilization for the testing of the serum, writing to Nichols: "If war comes I imagine we should have a good opportunity to get the matter settled in work with the troops next winter" (Rufus Cole to Henry Nichols, 3/26/17 [RCP]).

24. Avery et al., *Acute Lobar Pneumonia,* 61.

25. W. W. Herrick, "Serum Treatment and Management of Lobar Pneumonia," *Medical Record* 99 (1921): 949.

26. Henry Chickering to Rufus Cole, 9/13/17 [RCP].

27. E. H. Buttles, "Pneumonia and Serum Therapy," *Vermont Medicine* 3 (1918): 30. See also Hans Zinsser to H. C. Michie, 10/23/17; Theodore C. Janeway to "Commanding Officer, Base Hospital, Camp Grant, Rockford, Illinois," 10/27/17 [both in RG112, Entry 31C, Box 100, Folder 710]; Henry Chickering to Rufus Cole, 2/28/18 [RCP].

28. See Peyton C. Marsh, "Special Orders, # 118," 5/20/18 [RCP, filed under "U.S. Army Material"].

29. Nichols, "The Lobar Pneumonia Problem in the Army," 154. Other published sup-

port from those serving in the military included Henry M. Thomas, "Pneumonia at Camp Meade, Maryland," *Journal of the American Medical Association* 71 (1918): 1307–10; Warren T. Vaughan and Truman G. Schnabel, "Pneumonia and Empyema at Camp Sevier," *Archives of Internal Medicine* 22 (1918): 440–65; W. R. Redden, "Development of Specific Serum Therapy in Pneumonia," *United States Naval Medical Bulletin* 13 (1919): 35–43; and L. W. McGuire, "Serum Treatment of Pneumonia," *Boston Medical and Surgical Journal* 186 (1922): 389–90.

30. See Willard J. Stone, Bruce G. Phillips, and Walter P. Bliss, "A Clinical Study of Pneumonia Based on Eight Hundred and Seventy-One Cases," *Archives of Internal Medicine* 22 (1918): 409–39; Joseph E. McClelland, "Determination of Type and Serum Treatment in Pneumococcus Infections," *Cleveland Medical Journal* 17 (1918): 226–30; Charles F. Tenney and William T. Rivenburgh, "A Group of Sixty-Eight Cases of Type I Pneumonia Occurring in Thirty Days at Camp Upton: With Special Reference to Serum Treatment," *Archives of Internal Medicine* 24 (1919): 545–52; and Simon S. Leopold, "Pneumonia and Empyema at Camp Dix," *New York Medical Journal* 110 (1919): 578–80.

31. J. E. Paullin, in Graham E. Henson, "Serum Therapy in Lobar Pneumonia, with Report of 67 Cases," *Southern Medical Journal* 13 (1920): 183.

32. For a vivid depiction of the epidemic and of the efforts of scientists and clinicians to combat it, see John M. Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History* (New York: Viking, 2004). While I disagree with a good deal of Barry's characterization of the Rockefeller efforts with respect to the pneumococcus (efforts that I would argue were shaped well before the advent of the influenza epidemic), I appreciate the palpable sense of therapeutic urgency emanating from his text.

33. Regarding normal serum, see J. H. Cannon, "Plain Human Serum Treatment of Pneumonia," *Southern Medical Journal* 12 (1919): 523–26. It was thought that the complement contained in the serum would augment the effects of naturally occurring antibodies. Regarding convalescent serum, see L. W. McGuire and W. R. Redden, "Treatment of Influenza Pneumonia by the Use of Convalescent Human Serum," *Journal of the American Medical Association* 71 (1918): 1311.

34. John H. McClellan, "Antipneumococcus Serum (Kyes) in the Treatment of Lobar Pneumonia," *Journal of the American Medical Association* 72 (1919): 1885; Alfred W. Gray, "Antipneumococcus Serum (Kyes's) in the Treatment of Pneumonia," *American Journal of Medical Science* 159 (1920): 885–91. Such serum was obtained from Preston Kyes at the University of Chicago, who in 1911 had generated seemingly effective antiserum, and whose treatment would continue to be advocated by isolated practitioners throughout the history of antipneumococcal serotherapy. See Preston Kyes, "The Production of Antibodies to Pneumococci in an Insusceptible Host," *Journal of the American Medical Association* 56 (1911): 1878–81; William E. Cary, "Use of Polyvalent Antipneumococcus Serum, Kyes," *Archives of Pathology* 26 (1938): 147–50.

35. Stone, Phillips, and Bliss, "A Clinical Study of Pneumonia," 429. Such serum was obtained from Edward C. Rosenow at the Mayo Clinic. See E. C. Rosenow, "Partially Autolyzed Pneumococci in the Treatment of Pneumonia," *Journal of the American Medical Association* 70 (1918): 759–63.

36. The one "controlled" study, obtained through the restriction of serum administra-

tion to a single ward when a shortage of supplies was at hand, was actually made with polyvalent chicken serum and revealed a nearly two-thirds reduction in mortality. See Gray, "Antipneumococcus Serum (Kyes's) in the Treatment of Pneumonia," 885–91.

37. Alvah Lewis Sawyer, "Last Word in Treatment of Pneumonia," *Illinois Medical Journal* 35 (1919): 71.

38. Rufus Cole to Simon Flexner, 2/18/18; see also Rufus Cole to Henry Chickering, 7/16/18 [both in RCP].

39. Henry Chickering to Rufus Cole, 10/10/18 [RCP]. Cole was well aware of such conditions. See Rufus Cole to Simon Flexner, 5/26/36 [RCP, filed under "Welch, William"]; see also Barry, *The Great Influenza,* 189–90.

40. See, for example, Vaughan and Schnabel, "Pneumonia and Empyema at Camp Sevier," 440. An "almost incredible" number of *Staphylococcus aureus* pneumonias were likewise documented by Chickering at Camp Jackson; in Henry Chickering to Rufus Cole, 10/22/18 [RCP].

41. Russell L. Cecil, "Pneumonia and Empyema at Camp Upton, N.Y.," *Medical Clinics of North America* 2 (1918): 574; McClelland, "Determination of Type and Serum Treatment in Pneumococcus Infections," 227; Russell Cecil and H. F. Vaughan, "Report of Pneumonia Commission at Camp Wheeler for October 1918, to the Surgeon General, U.S. Army, Washington, D.C.," 11/21/18 [RCP, filed under "Cecil, Russell"]; Francis Blake to Rufus Cole, 11/22/18 [RCP].

42. Cecil, "Pneumonia and Empyema at Camp Upton, N.Y.," 581; Henson, "Serum Therapy in Lobar Pneumonia," 179.

43. Arthur Bloomfield, "The Effects of Serum Therapy in Acute Lobar Pneumonia," *Bulletin of the Johns Hopkins Hospital* 28 (1917): 306. See also Lawrence Litchfield to Rufus Cole, 3/28/17 [RCP]. Cole had dismissed the "excitement" of such reports as resulting from poor technique and exaggeration; see Rufus Cole to Lawrence Litchfield, 3/30/17 [RCP].

44. For parallels from the history of antidiphtherial antitoxin, see Hammonds, *Childhood's Deadly Scourge,* 122–23. Serum was certainly not overshadowed—as might be supposed—by efforts at preventive pneumococcal vaccination (discussed in chapter 8), which had been dealt an even harsher blow by equivocal wartime studies among recruits and which would remain markedly overshadowed by therapeutic antiserum throughout the ensuing quarter-century.

45. Francis Blake to Rufus Cole, 11/22/18 [RCP].

46. It is difficult to quantify the trend of serum usage during this era. Several prominent contemporary observers would cite its usage as widespread, particularly in large cities and where local typing facilities had been established. See C. P. Howard, "Treatment of Pneumonia with Special Reference to the Use of Serum," *Canadian Medical Association Journal* 11 (1921): 711; William S. Thomas, "Type I Pneumonia and its Serum Treatment," *Journal of the American Medical Association* 77 (1921): 2101; Russell L. Cecil, "Specific Prevention and Specific Treatment of Lobar Pneumonia," *Military Surgeon* 53 (1923): 466. Likewise, an equal number of qualified observers would declare its usage to be on the wane in the setting of the mixed wartime experience. See Edwin A. Locke, "The Treatment of Type I Pneumococcus Lobar Pneumonia with Specific Serum," *Journal of the American Medical Association* 80 (1923): 1507; Frederick T. Lord, "The Serum Treatment of Type I Pneumo-

coccus Pneumonia," *Medical Clinics of North America* 7 (1923): 775; Herrick, "Serum Treatment and Management of Lobar Pneumonia," 950.

47. Thomas, "Type I Pneumonia and its Serum Treatment," 2101; Locke, "The Treatment of Type I Pneumococcus Lobar Pneumonia," 1507.

48. See Locke, "The Treatment of Type I Pneumococcus Lobar Pneumonia," 1511.

49. Cole, in apparent response to a request from Thomas, had sent Thomas reprints of at least five pneumonia studies, which Thomas later failed to cite, and had written (apparently, in vain) to offer his assistance in person to Thomas nearly three months prior to the publication of Thomas's article. See Rufus Cole to William Thomas, 10/6/21 [RCP]. Cole had likewise consulted with Locke regarding the establishment of Boston City Hospital's own pneumonia service (Rufus Cole to Warren Vaughan, 7/28/19 [RCP]). For Cole's incredulity regarding the data presented in Thomas's and Locke's papers, see Rufus Cole to Augustus Wadsworth, 5/24/23; Rufus Cole to Joseph Miller, 5/25/23; Rufus Cole to Arthur Bloomfield, 6/20/23 [all in RCP].

50. Rufus Cole to Frederick P. Gay, 5/25/23 [RCP].

51. Rufus Cole to F. Neufeld, 4/26/22; Rufus Cole to F. Neufeld, 10/3/21 [both in RCP].

52. Goldsborough, "A Contribution to the Treatment of Pneumonia with Antipneumococcic Serum," 1681; see also Washbourn, "Antipneumococcic Serum," 1849; Cole, "Treatment of Pneumonia by Means of Specific Serums," 663; Francis Blake, "Recent Advances in the Treatment of Pneumonia" ["Paper" given in Minneapolis in 1917], 5 [FBP]; Rufus Cole to F. Neufeld, 12/22/21 [RCP]. For parallels from the treatment of diphtheria, see Hammonds, *Childhood's Deadly Scourge*, 110.

53. Locke, "The Treatment of Type I Pneumococcus Lobar Pneumonia," 1510. At Boston City Hospital, none of twelve patients treated in the first three days of disease onset died. The overall halving in the mortality rate in Boston among patients treated within the first three days (to 9.1%), however, was tempered by the outlying finding of a 9.4 percent mortality rate among those treated on the fifth day of disease.

54. As one New York practitioner projected his wishes: "If I were allowed to prophesy, I would predict that the present method will be supplanted by one in which a concentrated serum free from the objectionable serum proteins, containing antibodies for all the recognized pathogenic types of pneumococci, and so doing away with the necessity for typing shall be developed" (Herrick, "Serum Treatment and Management of Lobar Pneumonia," 950).

55. F. M. Huntoon, "Antibody Studies. I. Reversal of the Antibody-Antigen Reaction," *Journal of Immunology* 6 (1921): 117–22; Lloyd D. Felton, "A Study of the Isolation and Concentration of the Specific Antibodies of Antipneumococcus Sera," *Boston Medical and Surgical Journal* 190 (1924): 819–25. Oswald Avery had in 1915 first identified the relationship between pneumococcal antibodies and the globulin fraction of horse serum, precipitating the antibodies with ammonium sulfate. See Oswald T. Avery, "The Distribution of the Immune Bodies Occurring in Antipneumococcus Serum," *Journal of Experimental Medicine* 21 (1915): 133–45. Avery's monovalent-therapy-advocating colleagues at the Rockefeller, upon noting the spate of publicity in both the New York and international newspapers over Felton's achievement, were quick to dismiss Felton's work as only a slight extension beyond Avery's own former study. See Rufus Cole to Michael Heidelberger, 5/23/24; Michael

Heidelberger to Rufus Cole, 6/8/24 [both in RCP]. Felton himself considered his standardization of antiserum units more important than his concentration of antiserum per se; see Lloyd D. Felton to Louis Dublin, 7/20/37 [LDP, Box 16, "Pneumonia"].

56. Of course, clinicians could likewise choose to ignore typing altogether in this setting. Concentrated polyvalent serotherapy, however, still had to vie with Cole's unconcentrated monovalent therapy and Felton's concentrated monovalent or bivalent therapy throughout the 1920s. Moreover, the reign of concentrated polyvalent serotherapy would be brief. As will be detailed in Part II, by the early 1930s, the pneumococci would be divided into thirty-two types. With polyvalent serum of more than a few types impossible to develop, and with simpler means of bedside typing introduced, emphasis returned to Cole's own ethos of necessary specificity.

57. *An Epoch in Life Insurance: A Third of a Century of Achievement: Thirty-Three Years of Administration of the Metropolitan Life Insurance Company* (New York: Metropolitan Life Insurance Company, 1924), 226–27. See also Milton J. Rosenau to Lee K. Frankel, 6/20/19; Lee K. Frankel to Milton J. Rosenau, 6/24/19 [both in LFP, Box 13]; Milton J. Rosenau to C. E. A. Winslow, 8/19/19 [CWP, Box 18]. As early as January of 1919, Frankel had warned of the excess mortality from pneumonia that had ensued for several years in the wake of the 1889 influenza epidemic, reminding his superintendents that "this fact is of extreme importance to us as an insurance company." See Lee K. Frankel, "To Superintendents and Detached Deputy Superintendents," 1/23/19 [LFP, Box 13]. Frankel appears to have been strongly motivated by humanitarian concerns as well.

58. Haley Fiske, "To the Home Office Staff," 9/24/19 [LFP, Box 13].

59. See Milton J. Rosenau to Lee K. Frankel, 7/16/19; Milton J. Rosenau to Lee K. Frankel, 4/20/20 [both in LFP, Box 13].

60. Ibid; Milton J. Rosenau to Lee K. Frankel, 4/22/21 [both in LFP, Box 13]. For a more modest view of the scope of the commission, see George W. McCoy (director of the U.S. Public Health Service's Hygienic Laboratory, and a commission member) to Milton J. Rosenau, 1/17/20 [LFP, Box 13].

61. See Milton J. Rosenau to Allan Freeman, 8/19/19; Milton J. Rosenau to Lee K. Frankel, 8/25/19; Lee K. Frankel to C. A. Craig, 9/18/19 [all in LFP, Box 13].

62. Regarding such national tracking, see Lee K. Frankel to George W. McCoy, 1/25/22 [LFP, Box 13]: "Apparently there is a marked increase in the number of [influenza] cases in New York. Have you any data for other cities? I have a feeling that the Influenza Commission should get together immediately and mobilize all agencies throughout the United States. Here is our chance." McCoy was much less optimistic in their capacity to influence events; see George McCoy to Lee K. Frankel, 1/26/22 [LFP, Box 13]. Regarding the cooptation of researchers (and of the University of Chicago's E. O. Jordan, in particular), see Lee K. Frankel to Milton J. Rosenau, 8/5/19; Milton J. Rosenau to Lee K. Frankel, 8/7/19 [both in LFP, Box 13].

63. Russell L. Cecil and Nils P. Larsen, "Clinical and Bacteriologic Study of One Thousand Cases of Lobar Pneumonia: With Special Reference to the Therapeutic Value of Pneumococcus Antibody Solution. Preliminary Report," *Journal of the American Medical Association* 79 (1922): 344, 345.

64. Russell L. Cecil and W. D. Sutliff, "The Treatment of Lobar Pneumonia with Con-

centrated Antipneumococcus Serum," *Journal of the American Medical Association* 91 (1928): 2036.

65. Ibid., 2040.

66. William H. Park, Jesse G. M. Bullowa, and Milton B. Rosenblüth, "The Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum," *Journal of the American Medical Association* 91 (1928): 1505.

67. Maxwell Finland, "The Serum Treatment of Lobar Pneumonia," *New England Journal of Medicine* 202 (1930): 1244–47. Finland found a reduction in mortality among type I cases from 31.4 percent to 21.3 percent and further noted that among twenty-two type I cases treated within three days of illness onset, not a single patient had died.

68. *Albany Evening News,* 31 December 1928, Box 17, Folder 156 [LLP].

Chapter 2. A "Specific" Specific and the Turbid Age of Applied Immunology

1. It is telling that Osler would nonetheless note: "A change of opinion has of late taken place as to the nature of pneumonia, which is now almost universally regarded as a specific infectious disease, depending upon a micro-organism" (*The Principles and Practice of Medicine* [New York: D. Appleton, 1892], 512). Perhaps his classification reflected his therapeutic rather than nosologic bias. By the third edition (1900), the section on pneumonia would appear in the infectious disease section of the book.

2. Osler, *Principles and Practice of Medicine,* 530. Osler's emphasis on the treatment of pneumonia as epitomizing the role of the *vis medicatrix naturae* had been expressed forcefully by him ten years earlier: "We now come to the important subject of the *treatment* of pneumonia, and the lessons you may learn from this should constitute your 'principia' in therapeutics. The *first* is that there is an inherent tendency in many diseases to recovery quite irrespective of any treatment. . . . The *second* lesson is that nature, in the majority of cases, is quite competent to restore the patient to health. . . . The *third* lesson is that the functions of the physician are to co-operate with Nature, to aid her where she fails, and, above all, to combat certain tendencies to a fatal issue, which tendencies are due either to an inherent or acquired viciousness of constitution, or the intensity of the inflammation" (William Osler, *Summer Session Clinics* [Montreal: Printed for a Committee of the Students, Gazette Printing and Publishing Company, 1882], Nos. 3 and 4, pp. 31–32). See also Michael Bliss, *William Osler: A Life in Medicine* (New York: Oxford University Press, 1999), 106–7.

3. John Harley Warner, *The Therapeutic Perspective: Medical Practice, Knowledge, and Identity in America, 1820–1885* (Cambridge, Mass.: Harvard University Press, 1986), 58–80. See also Martin Pernick, *A Calculus of Suffering: Pain, Professionalism, and Anesthesia in Nineteenth-Century America* (New York: Columbia University Press, 1985), 128–30; Charles E. Rosenberg, *The Care of Strangers: The Rise of America's Hospital System* (New York: Basic Books, 1987), 71–78.

4. Warner, *Therapeutic Perspective,* 235–83. For a contrasting account, detailing the persistence of such individualization, see Pernick, *Calculus of Suffering,* 125–47.

5. My use of the term "physiology-based rationalism" serves as a somewhat anachronistic amalgamation of two terms introduced by Warner to describe the post-1860s turn in

American medicine: "physiological therapeutics" (a historically accurate term), and "New Rationalism" (coined by Warner to describe the emerging ethos of the time). See Warner, *Therapeutic Perspective,* 243–57, in particular.

6. Ibid., 263.

7. Regarding the antecedent history of "specifics" as promulgated by Paracelsus in the sixteenth century and Thomas Sydenham in the seventeenth, see Edmund D. Pellegrino, "The Sociocultural Impact of Twentieth-Century Therapeutics," in *The Therapeutic Revolution: Essays in the Social History of American Medicine,* ed. Morris J. Vogel and Charles E. Rosenberg (Philadelphia: University of Pennsylvania Press, 1979), 248–51.

8. W. E. Hughes and W. S. Carter, "A Case of Pneumonia Treated by Transfusion of Blood from a Convalescent Case," *Therapeutic Gazette* 16 (1892): 668.

9. William H. Welch, "Discussion of Pneumonia," *Journal of the American Medical Association* 42 (1904): 1095. In 1892, despite his critical assessment of contemporary antipneumococcal serotherapy, Welch had noted with hope and perspicacity: "The future may succeed in surmounting difficulties which are now apparent. With a clearer understanding of the basis of immunity from the pneumococcus, means may be found to heighten the immunity" ("The Etiology of Acute Lobar Pneumonia, Considered from a Bacteriological Point of View," *Transactions of the Medical and Chiurgical Faculties of the State of Maryland, 94th Annual Session* [Baltimore, Md.: Griffin, Curley, and Company, 1892], 99, 100).

10. Rufus Cole, "Treatment of Pneumonia by Means of Specific Serums," *Journal of the American Medical Association* 61 (1913): 663.

11. Ibid., 665.

12. As a member of the U.S. Navy Medical Corps would write, in 1919, of the Rockefeller studies: "These results, now more or less universal, have placed Type I antipneumococcus serum in the class of specifics, and make it almost unpardonable for a practitioner to treat a case of pneumonia without attempting to work out the type, and to administer Type I serum if the organism be of that type" (W. R. Redden, "Development of Specific Serum Therapy in Pneumonia," *United States Naval Medical Bulletin* 13 [1919]: 36).

13. Joseph Eichberg, "The Serum Treatment of Pneumonia," *American Medicine* 3 (1902): 691.

14. Over twenty years later, Cole would retain this ethos: "The great advances made in the diagnosis of pneumonia by the introduction of methods of percussion at the beginning of the last century may have been almost as harmful as useful" ("Stenographic Notes of Discussion by Doctor Cole at the Conference of District State Health Officers on January 16, 1936" [RCP, filed under "Cole, RI, Notes for Articles"]).

15. Despite its admonition that "in addition to the specific therapy advised in the treatment of Pneumococcus Type I infections, the general hygienic and therapeutic management of the case must not be neglected," a mere three of the 110 pages of the Rockefeller Hospital's pneumonia monograph of 1917 was devoted to such general measures (Oswald T. Avery et al., *Acute Lobar Pneumonia: Prevention and Serum Treatment* [New York: Rockefeller Institute for Medical Research, 1917], 74–76). For the general reorientation of perspective in America toward disease specificity in the wake of the New Public Health Movement, see Barbara Gutmann Rosenkrantz, "Cart before Horse: Theory, Practice, and Professional Image

in American Public Health, 1870–1920," *Journal of the History of Medicine* 29 (1974): 72. Regarding the emerging "tyranny of diagnosis" arranged around such notions, see Charles E. Rosenberg, "The Tyranny of Diagnosis: Specific Entities and Individual Experience," *Milbank Quarterly* 80 (2002): 247.

Such transforming concepts of nosological specificity were by no means inevitable. In Great Britain, where antipneumococcal serotherapy failed to achieve popularity, patient characteristics remained central to the nosology and therapy of the disease. See Michael Worboys, "Treatments for Pneumonia in Britain, 1910–1940," in *Medicine and Change: Historical and Sociological Studies of Medical Innovation,* ed. Ilana Löwy (London: John Libbey and Company, Ltd., 1993), 318–20. Regarding the more problematic evolution between microbiological and nosological specificity as advanced in France and Germany at the time with respect to tuberculosis, see J. Andrew Mendelsohn, "Medicine and the Making of Bodily Inequality in Twentieth Century Europe," in *Heredity and Infection: The History of Disease Transmission,* ed. Jean-Paul Gaudillière and Ilana Löwy (London: Routledge, 2001), 21–79.

16. Cole's enormous investment in the redefinition of pneumonia may explain, in part, his persistent opposition to polyvalent antiserums. Offering a telling nosology of pneumococcal pneumonia diametrically opposed to Cole's, a practitioner from Chicago (which persisted as a bastion of polyvalent and nonspecific immunotherapy against pneumonia throughout the antiserum era), advocating Kyes's polyvalent serum, would, in supporting the "logical" basis of polyvalent serum, remark: "It is well known that the most constant characteristic of the pneumococcus is its ability to produce the same clinical picture in the patient regardless of its type" (William E. Cary, "Use of Polyvalent Antipneumococcus Serum, Kyes," *Archives of Pathology* 26 [1938]: 149).

17. Francis Blake, "Recent Advances in the Treatment of Pneumonia ["Paper" given in Minneapolis in 1917]," 2 [FBP].

18. Lawrence Litchfield, in Rufus Cole, "Report of Studies Concerning Acute Lobar Pneumonia," *Journal of the American Medical Association* 69 (1917): 508.

19. See Rufus Cole, "Acute Pulmonary Infections," *De Lamar Lectures, 1927–1928* (Baltimore: Williams and Wilkins Company, 1929), 2–5. Again revealing the persistence of a diametrically opposed approach to Cole's atomization of pneumonia, the chief medical officer of the United States Treasury Department had stated to the surgeon general two years before that "owing to the variety of organisms and causes giving rise to inflamation [*sic*] of the lungs, pneumonia must be regarded as a sign or symptom in the same way as rheumatism is today" (E. K. Sprague to Surgeon General, 2/11/26 [RG90 0425–32, Box 901].

20. Cole, "Acute Pulmonary Infections," 1–2.

21. Arthur M. Silverstein, "The Dynamics of Conceptual Change in Twentieth Century Immunology," *Cellular Immunology* 132 (1991): 521. In the "Immunotherapy" section of Debra Jan Bibel's otherwise excellent *Milestones in Immunology,* not a single paper is noted between Sir Almroth Wright's 1897 publication on vaccination against typhoid fever and Colin Macleod's 1945 publication on prophylactic vaccination against pneumonia.

22. Sinclair Lewis, *Arrowsmith* (New York: Grossett and Dunlap, 1925), 138–39. In many respects, Part I of this book represents an extended footnote to Lewis's brilliant contemporary examination (written with the assistance of Paul DeKruif) of the rise of scientific medicine in this country, and *Arrowsmith* continues to serve as a fascinating primary source

in its own right (albeit, to be taken with more than a few laboratory scale-measured grains of salt).

23. Regarding chemotherapy, a fictional example is again representative, as Martin Arrowsmith and Terry Wickett ultimately focus on the attack on the pneumococcus itself with quinine (*Arrowsmith,* 419–22). Regarding lactobacillus therapy, see Scott Podolsky, "Cultural Divergence: Elie Metchnikoff's *Bacillus bulgaricus* Therapy and His Underlying Conception of Health," *Bulletin of the History of Medicine* 72 (1998): 1–27. Regarding bacteriophage therapy, see William C. Summers, *Felix d'Herelle and the Origins of Molecular Biology* (New Haven, Conn.: Yale University Press, 1999); Karen Ho, "Bacteriophage Therapy for Bacterial Infections: Rekindling a Memory from the Pre-antibiotics Era," *Perspectives in Biology and Medicine* 44 (2001): 1–16.

24. Regarding meningitis, see Simon Flexner and J. W. Jobling, "Serum Treatment of Epidemic Cerebro-Spinal Meningitis," *Journal of Experimental Medicine* 10 (1908): 141–203; Simon Flexner and J. W. Jobling, "An Analysis of Four Hundred Cases of Epidemic Meningitis Treated with Anti-Meningitis Serum," *Journal of Experimental Medicine* 10 (1908): 690–733; Simon Flexner, "The Present Status of the Serum Therapy of Epidemic Cerebro-Spinal Meningitis," *Journal of the American Medical Association* 53 (1909): 1443–45; Simon Flexner, "The Results of the Serum Treatment in Thirteen Hundred Cases of Epidemic Meningitis," *Journal of Experimental Medicine* 17 (1913): 553–76; Kenneth D. Blackfan, "The Use of Antimeningococcus Serum in the Treatment of Epidemic Meningitis," *Journal of the American Medical Association* 76 (1921): 36–37; Harry F. Dowling, *Fighting Infection: Conquests of the Twentieth Century* (Cambridge, Mass.: Harvard University Press, 1977), 52–54. Regarding scarlet fever, see Augustus B. Wadsworth, "The Hemolytic Streptococci and Anti-Streptococcus Serum in Scarlet Fever," *American Journal of Public Health* 19 (1929): 1287–302; Harry F. Dowling, "Diphtheria as a Model: Introduction of Serums and Vaccines for Scarlet Fever and Pneumococcal Pneumonia," *Journal of the American Medical Association* 226 (1973): 551. Regarding poliomyelitis, see Naomi Rogers, *Dirt and Disease: Polio Before FDR* (New Brunswick, N.J.: Rutgers University Press, 1992), 96–103.

25. While antimeningococcal antiserum, for example, would be considered to have "revolutionized" treatment, such modalities as vaccines for the active treatment of gonorrhea, pertussis, and cholera would be deemed worthless.

26. Regarding the increasingly favorable view among scientists of applied science in general in the Progressive and post-Progressive eras, see John P. Swann, *Academic Scientists and the Pharmaceutical Industry: Cooperative Research in Twentieth Century America* (Baltimore: Johns Hopkins University Press, 1988), 41.

27. A. R. Dochez and L. J. Gillespie, "A Biologic Classification of Pneumococci by Means of Immunity Reactions," *Journal of the American Medical Association* 61 (1913): 727.

28. For evidence that Cole's ongoing determination was further fostered by the loss of colleagues to pneumonia, see Rufus Cole to William Moss, 1/2/17; Rufus Cole to G. Canby Robinson, 3/6/17 [both in RCP]. The 1917 Rockefeller monograph on the serum treatment of pneumonia would describe the biological investigations at the Institute as "a study of acute lobar pneumonia with the special object of improving methods of treatment" (Avery et al., *Acute Lobar Pneumonia: Prevention and Serum Treatment,* 5).

29. Olga Amsterdamska, "Between Medicine and Science: The Research Career of Oswald T. Avery," in *Medicine and Change: Historical and Sociological Studies of Medical Innovation,* ed. I. Löwy (London: John Libbey and Company, 1993), 185–86. See also Nicholas Russell, "Oswald Avery and the Origin of Molecular Biology," *British Journal for the History of Science* 21 (1988): 393–400.

30. Colin MacLeod, "Remarks at Dedication of Avery Memorial Gate," 9/29/65 [RCP, filed under "Macleod, Colin"]. See also Rufus Cole, "Presentation of the Kober Medal to Dr. Oswald T. Avery," *Transactions of the Association of American Physicians* 59 (1946): 39.

31. In this setting, a practitioner advocating to the Surgeon General his "white blood cell feeding" yeast extract as a "specific" for pneumonia "only equaled by the action of the specific serum in an early Diphtheria" would be politely ignored. See A. M. Wheeler to Surgeon General, 12/13/17; Earl H. Bruns to A. M. Wheeler, 12/22/17 [both in RG112, Box 402, Entry 29, Folder 713].

32. Bruce W. Goldsborough, "A Contribution to the Treatment of Pneumonia with Antipneumococcic Serum," *Journal of the American Medical Association* 38 (1902): 1681.

33. Edwin A. Locke, "The Serologic Treatment of Lobar Pneumonia," *Boston Medical and Surgical Journal* 190 (1924): 196. See also Hans Zinsser, "An Immunologic Consideration of Pneumonia and a Discussion of the Rational Basis for Vaccine Therapy," *New England Journal of Medicine* 200 (1929): 853.

34. Regarding the increasing emphasis placed on the development of a "rational" therapeutics in general throughout the era, see Harry M. Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (New York: Cambridge University Press, 1997), 17–28.

35. See Arthur M. Silverstein, *A History of Immunology* (San Diego, Calif.: Academic Press, 1989), 49–56; Alfred I. Tauber and Leon Chernyak, *Metchnikoff and the Origins of Immunology: From Metaphor to Theory* (New York: Oxford University Press, 1991), 149–74. William F. Petersen, one of the leading advocates of the role of nonspecific immunity in infection, would lament in 1922: "We are fairly well grounded in our knowledge of the specific factors of immunity. Our knowledge of the nonspecific elements is still decidedly fragmentary. Enthusiasm in one direction should not for an instant obscure our vision of all other possible factors in resistance" (*Protein Therapy and Nonspecific Resistance* [New York: Macmillan, 1922], 10).

36. E. C. Rosenow, "Partially Autolyzed Pneumococci in the Treatment of Pneumonia," *Journal of the American Medical Association* 70 (1918): 763.

37. Joseph Roby to Rufus Cole, 12/2/23 [RCP].

38. Graham E. Henson, "Serum Therapy in Lobar Pneumonia, with Report of 67 Cases," *Southern Medical Journal* 13 (1920): 178; Lewis A. Conner, "Experiences in New York Hospital with the Treatment of Lobar Pneumonia by a Serum-Free Solution of Pneumococcus Antibodies," *American Journal of Medical Science* 164 (1922): 843–44; Locke, "The Serologic Treatment of Lobar Pneumonia," 203. Cole had even resisted acknowledging the potentially nonspecific benefits of the equally potentially harmful chill reactions occurring during his own trials; see Rufus Cole to Simon Flexner, 2/27/17 [RCP]. Cole had likewise politely rejected a request from Hans Zinsser in 1916 to study the potential efficacy of non-

specific leukocyte extracts. See Hans Zinsser to Rufus Cole, 4/25/16; Rufus Cole to Hans Zinsser, 5/1/16 [both in RCP]. As late as 1933, Alexander Lambert reported his own successful controlled trial of active vaccine therapy at Bellevue, remarking that "it cannot all be laid to chance." William Park, in discussion, begged to differ. In Alexander Lambert, "Some Effects of Vaccines on Antibodies in Pneumonia," *Transactions of the Association of American Physicians* 43 (1933): 86, 87.

39. The dramatic phenomenon of the crisis was to be contrasted with that of "lysis," in which a patient would continue to remain febrile for an indefinite length of time after the initial reduction in temperature (with a slowly resolving clinical course, under ideal conditions). It was recognized that children and healthy adults were more likely to experience a crisis, while the more elderly and debilitated would experience the often less-successful lysis. See, e.g., Robert Bruce Preble, *Pneumonia and Pneumococcus Infections* (Chicago: C. J. Head and Company, 1905), 49–51.

40. See A. R. Dochez, "The Presence of Protective Substances in Human Serum During Lobar Pneumonia," *Journal of Experimental Medicine* 16 (1912): 665. Reflecting the emerging reformulation of pneumonia from an anatomical to a microbiological/immunological event, Paul Clough at Johns Hopkins asserted: "It is certain that the crisis is not due to an anatomical change in the diseased lung tissue" ("The Development of Antibodies in the Serum of Patients Recovering from Acute Lobar Pneumonia," *Bulletin of the Johns Hopkins Hospital* 24 [1913]: 295).

41. Dochez, "Presence of Protective Substances," 679.

42. F. Neufeld and W. Rimpau, "Weitere Mittheilungen über die Immunität gegen Streptokokken und Pneumokokken," *Zeitschrift für Hygiene und Infektionskrankheiten* 51 (1905): 283–99; as discussed in Clough, "The Development of Antibodies in the Serum of Patients Recovering from Acute Lobar Pneumonia," 296.

43. Ibid., 295–306.

44. Carroll G. Bull, "The Mechanism of the Curative Action of Antipneumococcus Serum," *Journal of Experimental Medicine* 22 (1915): 457–65.

45. Reflecting his own humoral versus cellular bias, Cole would surmise: "The observations I have mentioned, as well as unpublished observations made in this laboratory, indicate strongly that natural recovery in pneumonia is associated with the development of humoral immunity and probably occurs because of this development" ("The Neutralization of Antipneumococcus Immune Bodies by Infected Exudates and Sera," *Journal of Experimental Medicine* 26 [1917]: 472).

46. Bibel, *Milestones in Immunology,* 87–88. See M. Heidelberger and O. T. Avery, "The Soluble Specific Substance of Pneumococcus," *Journal of Experimental Medicine* 38 (1923): 73–79.

47. A. R. Dochez and O. T. Avery, "The Elaboration of Specific Soluble Substance by Pneumococcus During Growth," *Journal of Experimental Medicine* 26 (1917): 493.

48. Cole, "Neutralization of Antipneumococcus Immune Bodies by Infected Exudates and Sera," 473.

49. Francis G. Blake, "Antigen-Antibody Balance in Lobar Pneumonia," *Archives of Internal Medicine* 21 (1918): 779. Regarding Blake's military travels and travails, see Francis

Blake to Rufus Cole, 4/6/18; Francis Blake to Rufus Cole, 11/22/18 [both in RCP]; John M. Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History* (New York: Viking, 2004), 174–75, 336.

50. Blake, "Antigen-Antibody Balance in Lobar Pneumonia," 787–88.

51. Blake, "Recent Advances in the Treatment of Pneumonia," 11 [FBP]; William H. Park, Jesse G. M. Bullowa, and Milton B. Rosenblüth, "The Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum," *Journal of the American Medical Association* 91 (1928): 1505, 1506.

52. See Russell L. Cecil, "The Specific Treatment of Pneumonia," *Archives of Internal Medicine* 41 (1928): 306–7; Horace S. Baldwin, "The Clinical Course and Treatment of Pneumonia as Related to the Pneumococcus Type," *Medical Clinics of North America* 12 (1928): 682–83. Regarding the pneumococcal capsule, see Heidelberger and Avery, "Soluble Specific Substance of Pneumococcus," 78.

53. Jesse G. M. Bullowa, "Lobar Pneumonia Type II treated with Felton and Banzhof and Sobotka's Antibody Solution," *Medical Clinics of North America* 12 (1928): 704.

54. Regarding serotherapy in particular, Dochez expressed his hope that the principles derived from the treatment of pneumonia could be extended to the treatment of all bacterial disease. See Dochez and Gillespie, "A Biologic Classification of Pneumococci by Means of Immunity Reactions," 730. Regarding applied immunology in general, see John A. Kolmer, "The Role of Immunity in the Conduct of the Present War," *Journal of Immunology* 3 (1918): 371.

55. For attempts to depict the theoretical basis of serotherapy as logically prior to its actual efficacy, see Horace S. Baldwin and Russell L. Cecil, "The Rationale of Specific Therapy in Pneumococcus Pneumonia," *Journal of the American Medical Association* 87 (1926): 1711, 1715; Park, Bullowa, and Rosenblüth, "The Treatment of Lobar Pneumonia with Refined Antibacterial Serum," 1506.

56. Benjamin White, in Russell L. Cecil, "Recent Advances in the Specific Treatment of Pneumonia," *New England Journal of Medicine* 199 (1928): 424. Cecil, for his own part, was happy to credit the "immunologists . . . now working in the study of pneumonia" (Russell L. Cecil, "The Specific Treatment of Pneumonia," *Archives of Internal Medicine* 41 [1928]: 297). From the same year, see also John Kolmer, in F. M. Huntoon, "Treatment of Pneumonia with Pneumococcus Antibody Solution," *Journal of the Medical Society of New Jersey* 25 (1928): 12.

57. Even within the rising academic field of immunology, commercialism appears to have infiltrated in typically American fashion. For example, Carroll Bull, who had chaired the first department of immunology in America at Johns Hopkins in 1919 (after having worked at the Rockefeller from 1913–17), resigned from the American Association of Immunologists in 1923, angrily relating to Cole the degree to which the nascent field was becoming overrun with competing, fee-demanding societies. Cole, who had assumed the presidency of the association in 1921 with the explicit purpose of reining in the commercial influence within that society in particular, attempted to retain Bull as a model of the pure scientist: "Four or five years ago I felt that if the Society was ever going to amount to anything the control would have to be taken out of the hands of those who were commercializing the science and placed with those who were really interested in immunology from

the scientific and educational standpoint." He was unsuccessful. See Rufus Cole to Ludvig Hektoen, 2/15/21; Carroll Bull to Rufus Cole, 12/4/23; Rufus Cole to Carroll Bull, 12/12/23; Carroll Bull to Rufus Cole, 12/17/23 [all in RCP]. Much remains to be written of the rise of basic and applied immunology in America in this respect. Regarding Bull, and as an important first attempt, see Arthur M. Silverstein, "The Development of Immunology in America," *Federation Proceedings* 46 (1987): 240–43.

58. Jonathan Liebenau, *Medical Science and Medical Industry: The Formation of the American Pharmaceutical Industry* (Baltimore: Johns Hopkins University Press, 1987), 57–78; Louis Galambos and Jane Eliot Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895–1995* (New York: Cambridge University Press, 1995), 9–24; "Pneumonia-Prevention and Treatment" [undated booklet, likely published between 1917 and 1920, MA, R10–1.6.4].

59. Liebenau, *Medical Science and Medical Industry,* 67.

60. George M. Gould, "Advances All Along the Line!" *Mulford Digest* 1 (1912): 58.

61. Liebenau, *Medical Science and Medical Industry,* 63–64; Galambos and Sewell, *Networks of Innovation,* 18–19.

62. Silverstein, "The Development of Immunology in America," 242. Regarding Wright's development of vaccine therapy, see Zachary Cope, *Almroth Wright: Founder of Modern Vaccine-Therapy* (London: Nelson, Ltd., 1966), 39–61.

63. Cole, not surprisingly, wrote in 1917 to South Africa's F. Spencer Lister (Wright's former assistant and a co-discoverer, along with Neufeld and Cole, of the subtypes of the pneumococcus): "Our experiments give us no justification for vaccine treatment, indeed observations which we have lately made indicate that such vaccination may be harmful" (Rufus Cole to F. Spencer Lister, 1/19/17 [RCP]). For the general Rockefeller dismissal of vaccine therapy, see also Simon Flexner, "Biologic Therapy: General Considerations Regarding Serum and Vaccine Therapy," *Journal of the American Medical Association* 76 (1921): 33–34. Ironically, in the pre–World War I era, active vaccine therapy had itself been considered to epitomize "rational" therapeutics. See Peter Keating, "Vaccine Therapy and the Problem of Opsonins," *Journal of the History of Medicine and Allied Sciences* 43 (1988): 290. Regarding the post–World War I decline of vaccine therapy in Britain, see Michael Worboys, "Vaccine Therapy and Laboratory Medicine in Edwardian Britain," in *Medical Innovations in Historical Perspective,* ed. John V. Pickstone (Houndmills, Basingstoke, Hampshire: Macmillan, 1992), 101–2.

64. Edward P. Swift, "The Vaccine Treatment of Typhoid and Pneumonia," *Mulford Digest* 2 (1913): 144.

65. "Memorandum," 10/7/20 [MA, R10–1.6.2]. Despite scattered encouraging studies that would emerge in the 1920s as applied to pneumonia, Mulford's efforts would ultimately prove fruitless. By the end of the 1920s, active vaccine therapy appears to have been greatly restricted in the United States. For the encouraging studies, see Alexander Lambert, "The Use of Mixed Stock Vaccines in Pneumonia," *Transactions of the Association of American Physicians* 41 (1926): 224–30; Don C. Sutton, "Vaccine Therapy in Pneumonia: A Preliminary Report," *Illinois Medical Journal* 53 (1928): 280–82. For the restriction in usage of active vaccine therapy, see Ludvig Hektoen and Ernest E. Irons, "Vaccine Therapy: Results of a Questionnaire to American Physicians," *Journal of the American Medical*

Association 92 (1929): 864–69; Keating, "Vaccine Therapy and the Problem of Opsonins," 294. Hektoen and Irons' account was based on extensive survey data. For a contrasting though far more impressionistic account of contemporary active vaccine usage, see Ralph A. Kinsella, "The Clinical Value of Serums and Vaccines," *Journal of the American Medical Association* 93 (1929): 1524–26.

66. Such polyvalent serum was still unconcentrated in the pre-Huntoon era.

67. "Pneumonia—Prevention and Treatment," 2 [MA, R10–1.6.4]; see also "Mulford Working Bulletin Number 7: Pneumonia Serums and Bacterins," 12 [MA, R10–1.6.2]. More ominously, Cole was particularly offended by Mulford's misuse of his name in promoting the use of especially large doses of serum on the first day of disease. To Mulford's A. Parker Hitchens, he wrote: "It is quite evident that my fears concerning the use of my name in connection with the serum which you are making was not entirely unfounded." The statement was apparently omitted from future publications. See A. Parker Hitchens, "The Scientific Basis for the Use of Antitoxins and Vaccines," *Mulford Digest* 2 (1914): 219; Rufus Cole to A. Parker Hitchens, 11/23/14; A. Parker Hitchens to Rufus Cole, 1/15/15 [both in RCP]. For a parallel instance of the misuse of a respected scientist's name in pharmaceutical advertisements, see John Swann's discussion of John Jacob Abel, in *Academic Scientists and the Pharmaceutical Industry,* 32–33.

68. "Mulford Working Bulletin Number 7," 77 [MA, R10–1.6.2].

69. A. Parker Hitchens, "Concerning Antipneumococcus Serum," accompanying Lawrence Litchfield to Rufus Cole [undated, RCP, filed under "Litchfield, Lawrence"]. Litchfield would also forward to Cole a letter from the Lederle Laboratories in which the director of its Antitoxin Lab—ignoring Cole's entire ethos of specificity—would justify the production of polyvalent serum along similar lines, concluding that "from the standpoint of saving human lives more good would be done with the serum as we prepared it than would be accomplished by preparing the antiserum for type I only." In S. D. Beard to Lawrence Litchfield, 3/15/17 [RCP, filed under "Litchfield, Lawrence"].

70. Rufus Cole to Lawrence Litchfield, 3/21/17 [RCP]. Regarding the broad tradition of academic medical scientists' monitoring of the products of commercial houses, see Marks, *Progress of Experiment,* 32–35.

71. Lawrence Litchfield to Rufus Cole, 3/28/17 [RCP].

72. Cole, upon analyzing a batch of serum for Eli Lilly and Company in 1917, would send it back to its director of biology with the harsh conclusion that "it is difficult to see how this serum could be of any therapeutic use whatever" (Rufus Cole to W. Showalter, 3/13/17 [RCP]).

73. "Memorandum," 1/24/18 [MA, R10–1.6.2]. Cf. with citation from Mulford Working Bulletin #8, dating from 1910, in Liebenau, *Medical Science and Medical Industry,* 77. For earlier attempts by commercial interests to besmirch diphtheria antitoxin produced by the Massachusetts State Board of Health, see Barbara Rosenkrantz, *Public Health and the State: Changing Views in Massachusetts, 1842–1936* (Cambridge, Mass.: Harvard University Press, 1972), 125.

74. "Memorandum," 1/9/19 [MA, R10–1.6.2].

75. "Memorandum," 9/25/19 [MA, R10–1.6.2].

76. Compare the earlier disapproving evaluations of the commercial sera by his col-

leagues (Francis Blake to Rufus Cole, 12/18/17; Henry Chickering to Rufus Cole, 7/7/18 [both in RCP]) with Cole's own eventual satisfaction with the sera: "I think that practically all the serum being sold by the reliable commercial houses at present is of good standard potency" (Rufus Cole to Eugene C. Kelley, 8/1/18 [RCP]).

77. Swann, *Academic Scientists and the Pharmaceutical Industry,* 35–41; Nicolas Rasmussen, "The Drug Industry and Clinical Research in Interwar America: Three Types of Physician Collaborator," *Bulletin of the History of Medicine* 79 (2005): 50–80.

78. With respect to applied immunology generally, see Liebenau, *Medical Science and Medical Industry,* 67–78. With respect to antipneumococcal serotherapy, compare the concerns of Cole, Blake, Thomas, and Locke in the wake of World War I (as discussed in chapter 1) with the promotions from Mulford: "While antipneumococcus serum has been successfully employed by the medical profession of America since its introduction, it was reserved for the medical corps U.S.A. to emphasize its real value and importance when administered in sufficient doses and early in the attack. Thousands of physicians returning from the Army and Navy to private practice were much impressed with the uniformly good results obtained in the hospitals and cantonments, both in France and America, in protecting the lives of American soldiers and sailors. In future they will doubtless regard antipneumococcus serum as one of the first lines of defense against the pneumococcal pneumonias and equal in specific value to Mulford's Diphtheria Antitoxin in the treatment of diphtheria" ("Pneumonia—Prevention and Treatment," 3 [MA, R10–1.6.4]).

79. For example, a Mulford "Working Bulletin" declared: "Containing as it does, antibodies against Types II, III, and IV [with 'and IV' later crossed out] as well as against Type I, it is logical to infer that the use of the polyvalent serum will show a larger average of cures than can be obtained from the employment of Type I serum" ("Mulford Working Bulletin Number 7," 14–15 [MA, R10–1.6.2]).

Chapter 3. Fundamental Tensions

1. Pierre-Charles-Alexandre-Louis, *Researches on the Effects of Bloodletting in Some Inflammatory Diseases; and on the Influence of Tartarized Antimony and Vesication in Pneumonitis,* trans. C. G. Putnam (Boston: Hilliard, Gray, and Company, 1836); see also J. Rosser Matthews, *Quantification and the Quest for Medical Certainty* (Princeton, N.J.: Princeton University Press, 1995), 14–20.

2. J. C. Wilson, "Serum Therapy in Croupous Pneumonia," *Journal of the American Medical Association* 35 (1900): 596. Such a viewpoint still differed markedly from the equation of therapeutic individuation with the "impossibility" of statistically analyzing the treatment of pneumonia, as expressed over three decades previously by William Aitken in *The Science and Practice of Medicine, From the 4th London Edition, with Additions,* ed. Meredith Clymer (Philadelphia: Lindsay and Blakiston, 1866), 2:745–46.

3. See, for example, Abraham M. Lilienfeld, "*Ceteris Paribus:* The Evolution of the Clinical Trial," *Bulletin of the History of Medicine* 56 (1982): 4–9.

4. Regarding Fibiger, compare Asbørn Hróbjartsson, Peter C. Gøtzsche, and Christian Gludd, "The Controlled Clinical Trial Turns 100 Years: Fibiger's Trial of Serum Treatment of Diphtheria," *British Medical Journal* 317 (1998): 1243; with Lilienfeld, who relates that

every other patient was treated ("*Ceteris Paribus,*" 11). Regarding Pearson, see Matthews, *Quantification and the Quest for Medical Certainty,* 89–94; Eileen Magnello, "The Introduction of Mathematical Statistics into Medical Research: The Roles of Karl Pearson, Major Greenwood, and Austin Bradford Hill," in *The Road to Medical Statistics,* ed. Eileen Magnello and Anne Hardy (New York: Rodopi, 2002), 95–123.

5. Lilienfeld notes, between 1900 and 1930, "the beginning of an appreciation of the need for controls and a gradually increasing refinement in experimental design" ("*Ceteris Paribus,*" 11).

6. See Walter W. Holland, Ellie Breeze, and Anthony V. Swan, "Clinical Trials: Some Reflections," *Statistics in Medicine* 1 (1982): 363; Peter Armitage, "Bradford Hill and the Randomized Controlled Trial," *Pharmaceutical Medicine* 6 (1992): 27. Hróbjartsson et al. write: "Unfortunately, Fibiger's methodological innovation had surprisingly little impact. The importance of random allocation was first fully recognised after the contribution of Fisher in 1925 and Bradford Hill in 1948" ("The Controlled Clinical Trial Turns 100 Years," 1245). And Richard Doll writes: "When I qualified in medicine in 1937, new treatments were almost always introduced on the grounds that in the hands of professor A or in the hands of a consultant in one of the leading teaching hospitals, the results in a small series of patients (seldom more than 50) had been superior to those recorded by professor B (or some other consultant) or by the same investigator previously" ("Controlled Trials: The 1948 Watershed," *British Medical Journal* 317 [1998]: 1217). For a more nuanced reevaluation of the era, focusing on the advent of 'blinding' in particular, see Ted J. Kaptchuk, "Intentional Ignorance: A History of Blind Assessment and Placebo Controls in Medicine,: *Bulletin of the History of Medicine* 72 (1998): 420–33.

7. Harry Dowling, "Emergence of the Cooperative Clinical Trial," *Transactions and Studies of the College of Physicians of Philadelphia* 43 (1975): 21–22; Harry M. Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (New York: Cambridge University Press, 1997), 53–60; Nicolas Rasmussen, "The Drug Industry and Clinical Research in Interwar America: Three Types of Physician Collaborator," *Bulletin of the History of Medicine* 79 (2005): 50–80; Desiree Cox-Maksimov, "The Making of the Clinical Trial in Britain, 1910–1945: Expertise, the State, and the Public" (Ph.D. thesis, Cambridge University, 1997); Matthews, *Quantification and the Quest for Medical Certainty,* 115–30.

Pearl, it should be noted, published his re-analysis of a World War I camp pneumonia study in 1919 to demonstrate the need for increased statistical sophistication among the American medical profession. As he quipped: "It is not too much to say that the investigator in the field of medicine should be as familiar with the probable error test as he is with the Wasserman test" (Raymond Pearl, "A Statistical Discussion of the Relative Efficacy of Different Methods of Treating Pneumonia," *Archives of Internal Medicine* 24 [1919]: 403). In response to a criticism of the paper by Cole himself, Pearl replied: "My little note demonstrates with mathematical precision an entire certainty—a certainty which cannot be shaken by anyone's opinion, however great his knowledge in non-statistical fields may be. . . . I am a statistician by profession, and I believe that modern statistical methods have great usefulness in all branches of science, in helping people to draw correct conclusions from observed facts. There are many people in the world, however, who have a profound

conviction that everything, or nearly everything, set forth in the form of numerical statistics is necessarily and inherently unreliable, and probably wrong. . . . It seems to me that if the general subject of medical statistics is to advance, or if the statistician is to render the aid which I believe he can to the medical man, they must thoroughly understand each other's point of view" (Raymond Pearl to Rufus Cole, 7/21/19 [RCP]).

8. "There was general dissatisfaction amongst the medical profession with the long series of reports on the serum treatment of pneumonia until the advent of the sulfonamides" (Lilienfeld, "*Ceteris Paribus,*" 11). Marks contributes a cogent analysis (though one that will be challenged to some extent in chapter 4) of the Massachusetts and New York Pneumonia Control Programs of the 1930s as examples of further collaborative efforts (thwarted, in his opinion, by the reluctance of private practitioners to apply the resulting "rational therapeutics"), but he largely ignores the earlier pneumonia collaborative efforts. See Marks, *Progress of Experiment,* 60–67.

9. "This issue of serum treatment of pneumonia stimulated the first collaborative trial that has been found reported in the literature. It was described in 1934 by the Therapeutic Trials Committee of the Medical Research Council in Great Britain" (Lilienfeld, "*Ceteris Paribus,*" 12). See also Doll, "Controlled Trials: The 1948 Watershed," 1217. As an exception, Harry Dowling draws brief attention to American antipneumococcal antiserum studies in "The Emergence of the Cooperative Clinical Trial," 20–21.

10. For diphtheria antitoxin evaluation in America in the pre-Fibiger era, see Evelynn Maxine Hammonds, *Childhood's Deadly Scourge: The Campaign to Control Diphtheria in New York City, 1880–1930* (Baltimore: Johns Hopkins University Press, 1999), 131–35. Regarding the paucity of subsequent controlled trials in the setting of the general belief in the efficacy of antitoxin, "the personal experiences and impressions of innumerable physicians," see Frederick W. Andrewes, William Bulloch, S. R. Douglas, et al., *Diphtheria: Its Bacteriology, Pathology, and Immunology* (London: His Majesty's Stationery Office, 1923), 265; W. W. C. Topley and G. S. Wilson, *The Principles of Bacteriology and Immunity* (New York: William Wood and Company, 1929), 2:870–73.

11. In response to Raymond Pearl's paper cited above, Cole would write to Flexner: "I think Pearl's paper simply demonstrates the danger of persons juggling with figures when they have no experience with the facts on which they are based. . . . No doubt the mathematics portion is perfect. As propaganda for the 'biometric method' I think a better example might be obtained" (Rufus Cole to Simon Flexner, 7/1/19). See also Rufus Cole to Simon Flexner, 7/23/19; Simon Flexner to Rufus Cole, 7/26/19 [all in RCP].

12. Rufus Cole, "Report of Studies Concerning Acute Lobar Pneumonia," *Journal of the American Medical Association* 69 (1917): 509. See also Rufus Cole to William S. Thomas, 10/6/21 [RCP].

13. See, for example, Lewis A. Conner, "Experiences in New York Hospital with the Treatment of Pneumonia by a Serum-Free Solution of Pneumococcus Antibodies," *American Journal of Medical Science* 164 (1922): 833. Arthur Bloomfield, at Johns Hopkins, noted that "at the present rate, years may elapse before an adequate series will be on record, and it seems highly desirable to obtain data on the value of the serum from other points of view" ("The Therapeutic Value of Type I Antipneumococcus Serum," *Journal of the American Medical Association* 81 [1923]: 1437). See also Rufus Cole to Arthur Bloomfield, 6/20/23 [RCP].

14. See, for example, Francis G. Blake, "Recent Advances in the Treatment of Pneumonia ["Paper" given in Minneapolis in 1917]," 15–17 [FBP].

15. Alexander Lambert, in Russell L. Cecil and Nils P. Larsen, "Clinical and Bacteriologic Study of One Thousand Cases of Lobar Pneumonia: With Special Reference to the Therapeutic Value of Pneumococcus Antibody Solution. Preliminary Report," *Journal of the American Medical Association* 79 (1922): 349.

16. Leo Kessell and Harold T. Hyman, "The Treatment of Lobar Pneumonia in a General Hospital," *Journal of the American Medical Association* 88 (1927): 1703.

17. Rufus Cole, "Serum Treatment in Type I Lobar Pneumonia," *Journal of the American Medical Association* 93 (1929): 742–43.

18. Ibid., p. 742.

19. Alfred W. Gray, "Antipneumococcus Serum (Kyes's) in the Treatment of Pneumonia," *American Journal of Medical Science* 159 (1920): 886.

20. Ibid., 887–88. Gray reported a mortality of 16.7 percent among 234 serum-treated cases, compared with a mortality of 53.6 percent among 1,684 control cases; see also Alfred W. Gray, "Antipneumococcus Serum (Kyes') in the Treatment of Pneumonia," 8/26/19 [RG112, Entry 31C, Box 99, Folder 710.1].

21. Kyes reported a mortality of 20.8 percent among the serum-treated cases, compared with 45.3 percent among control cases ("The Treatment of Lobar Pneumonia with an Anti-Pneumococcus Serum," *Journal of Medical Research* 38 [1918]: 495–501). The New York pneumonia specialists never appear to have taken too seriously the results with Kyes's serum. Cole wrote to Kyes in 1919: "I have been much interested in the clinical reports which appeared concerning the use of chicken serum, and I should like very much indeed to make a few observations with this serum. . . . I am taking it for granted that your work has reached the stage now where you would be quite willing to let us make some observations" (Rufus Cole to Preston Kyes, 5/23/19 [RCP]). It is unclear if Kyes actually sent Cole a sample.

22. C. J. Fishman, in L. A. Mitchell, "A New Treatment in Pneumonia," *Journal of the Oklahoma State Medical Association* 16 (1923): 392.

23. Edwin A. Locke, "The Treatment of Type I Pneumococcus Lobar Pneumonia with Specific Serum," *Journal of the American Medical Association* 80 (1923): 1507. This ethos was likewise articulated by Walter Niles, at Bellevue, where Cecil would commence his work. See Walter L. Niles, "The Serum Treatment of Lobar Pneumonia," *New York Medical Journal* 113 (1921): 872.

24. Draft copy of Lee K. Frankel, "To the Home Office Staff," 9/24/19 [LFP, Box 13]. Two copies of the draft exist in the archive; one is further annotated in the section under consideration, though without important substantive differences.

25. "We shall, I think, be able to control everything quite satisfactorily since we are getting the cordial cooperation of all officials. . . . The Secretary of the [Illinois] State Board of Health, who has interested himself warmly in the work of public institutions, has suggested that there are a number of communities in which he thinks it would be possible to vaccinate approximately half the population and to get proper control and full and accurate reports" (E. O. Jordan to Milton J. Rosenau, 11/10/19). See also George W. McCoy to Mil-

ton J. Rosenau, 1/17/20; E. O. Jordan to Milton J. Rosenau, 1/15/20 [all in LFP, Box 13]. Certainly more research is warranted to place such "controlled" vaccination efforts, along with peri–World War I efforts against influenza, in the context of the overall evolution of the controlled trial in America.

26. Milton J. Rosenau to Lee Frankel, 4/22/21 [LFP, Box 13]. See also William H. Park, Jesse G. M. Bullowa, and Milton B. Rosenblüth, "The Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum," *Journal of the American Medical Association* 91 (1928): 1503.

27. Cecil and Larsen, "Clinical and Bacteriologic Study of One Thousand Cases of Lobar Pneumonia," 344.

28. F. M. Huntoon, in ibid., 348. Huntoon also lauded the "cooperation of institutions for scientific interest," noting that "five different institutions had combined resources to gain something of possible scientific value."

29. Wade W. Oliver and E. A. Stoller, "Notes on the Therapeutic Value of Pneumococcus Antibody Solution Subcutaneously Administered in Lobar Pneumonia," *Archives of Internal Medicine* 35 (1925): 267. Edwin A. Locke noted before the Philadelphia County Medical Society in November of 1923: "During the coming winter the antibody solution is to be carefully tested therapeutically in large hospitals in New York, Philadelphia, Boston, Cincinnati and Chicago under uniform methods formulated by the Influenza Commission of the Metropolitan Life Insurance Company (Drs. Rosenau, Park and McCoy)" ("The Serological Treatment of Lobar Pneumonia," *Boston Medical and Surgical Journal* 190 [1924]: 203). No published studies would emerge from the Philadelphia, Cincinnati, or Chicago hospitals, and it is unclear if studies were indeed conducted there.

30. Unfortunately, the correspondence in the Frankel collection regarding the internal discussions of the Influenza Commission inexplicably ends in early 1922, though the commission would continue its activities throughout the decade. I have not been able to locate the commission's proceedings elsewhere, including among the Milton Rosenau papers at the University of North Carolina. For the persistence of the Influenza Commission throughout the antipneumococcal serotherapeutic era, see Lewis Ryers Thompson to Donald B. Armstrong, 4/19/37; Donald B. Armstrong to Lewis Ryers Thompson, 4/21/37 [RG443 0425, Box 14].

31. Jesse G. M. Bullowa, "Use of Antipneumococcic Refined Serum in Lobar Pneumonia: Data Necessary for a Comparison between Cases Treated with Serum and Cases Not So Treated, and the Importance of a Significant Control Series of Cases," *Journal of the American Medical Association* 90 (1928): 1354.

32. Ibid., 1355–56. Based on the severity ratings (which failed to achieve popularization), and in anticipation of the PORT scores devised nearly seventy years later, Bullowa derived a nearly linear relationship between the admission ratings and overall mortality among all cases. Regarding the PORT scoring system, see Michael J. Fine, Thomas E. Auble, and Donald M. Yealy, "A Prediction Rule to Identify Low-Risk Patients with Community-Acquired Pneumonia," *New England Journal of Medicine* 336 (1997): 243–50.

33. Bullowa, "Use of Antipneumococcic Refined Serum in Lobar Pneumonia," 1354.

34. Ibid., 1357.

35. Jesse G. M. Bullowa, "The Control," *Bulletin of the New York Academy of Medicine* 4 (1928): 341.

36. Taking, for example, p = the mortality rate among the treatment group, q = 1 − p, and n = the number of patients enrolled in the treatment group, a standard error, E, could be derived as the square root of pq/n (thus, the larger the study population, the smaller the standard error). Upon obtaining the standard errors for both the treatment and control groups, a standard error of difference, SED, could be obtained, equal to the square root of the sum of the squares of the individual standard errors. In actuality, a ratio of 1.96 should be used to attain statistical significance to the 95 percent confidence level. For contemporary biometric methodology, see Raymond Pearl, *Introduction to Medical Biometry and Statistics* (Philadelphia: W. B. Saunders, 1923), 209–19.

37. Bullowa would also use the cooperative nature of the studies to demonstrate that by combining his results with Cecil's, he could similarly achieve statistical significance. However, in combining his results with Cecil's, he would offset the type II benefits noted in Cecil's study, resulting in an overall nonsignificant benefit for type II serum (Park, Bullowa, and Rosenblüth, "The Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum," 1505).

38. John Wyckoff, Eugene F. Dubois, and I. Ogden Woodruff, "The Therapeutic Value of Digitalis in Pneumonia," *Journal of the American Medical Association* 95 (1930): 1243; Lilienfeld, "*Ceteris Paribus*," 11.

39. The British report begins: "During the last three years the Medical Research Council have assisted an inquiry at different centres in Great Britain into the therapeutic value of specific sera for lobar pneumonia, following the great development of similar work in the United States" ("The Serum Treatment of Lobar Pneumonia: A Report of the Therapeutic Trials Committed of the Medical Research Council," *British Medical Journal* 1 [1934]: 241). See also Alan Yoshioka, "Use of Randomization in the Medical Research Council's Clinical Trial of Streptomycin in Pulmonary Tuberculosis in the 1940s," *British Medical Journal* 317 (1998): 1221. Peter Armitage identifies A. Bradford Hill as the actual source of the statistical section of the Therapeutic Trial Committee's antipneumococcal serotherapy report but forgoes any mention of potential American influence by instead drawing a direct lineage from Karl Pearson to Major Greenwood to Hill (Armitage, "Bradford Hill and the Randomized Controlled Trial," 27). Cf. the minimization of Hill's input at this stage by Maksimov, "The Making of the Clinical Trial in Britain," 205. Indeed, Maksimov describes the "ubiquitous" employment of "alternation" and "control" in the interwar period, taking them as a conceptual granted without documenting on what basis they became more commonly employed by the early 1930s (ibid., 203).

40. In Bullowa's 1937 textbook on pneumonia, he would initiate the chapter on serum therapy with a 13-page exegesis of the statistical methods underlying the evaluation of such therapy (*The Management of the Pneumonias* [New York: Oxford University Press, 1937], 285–98. That same year, Hill would publish in *Lancet* his own extended presentation on the use of statistics in medicine, to be collected in the text, *Principles of Medical Statistics* (London: The Lancet Limited, 1937). Bullowa and his colleagues actually received statistical assistance from Met Life, since Louis Dublin (vice president and statistician) and his staff helped analyze the data emerging from the Harlem Hospital studies.

41. Sinclair Lewis, *Arrowsmith* (New York: Grossett and Dunlap, 1925), 41.

42. Dwight O'Hara, "Pneumococcus Lobar Pneumonia," *New England Journal of Medicine* 209 (1933): 223.

43. Maxwell Finland, "The Serum Treatment of Lobar Pneumonia," *New England Journal of Medicine* 202 (1930): 1246. As detailed throughout Part III, Finland would remain both a leader of numerous serotherapy trials and a persistent gadfly regarding the validity of such trials' results.

44. Randolph Lyons, in E .L. Walker, "Lobar Pneumonia and its Treatment," *New Orleans Medical and Surgical Journal* 84 (1931): 374. See also H. J. Lehnhoff, in F. A. McGrew, "A Rational Treatment of Pneumonia," *Nebraska State Medical Journal* 8 (1923): 323; Tinsley R. Harrison, in Henry T. Chickering, "The Prognosis and Treatment of Lobar Pneumonia," *Southern Medical Journal* 23 (1930): 115. Regarding antebellum aspects of such regionalism, see John Harley Warner, "The Idea of Southern Medical Distinctiveness: Medical Knowledge and Discourse in the Old South," in *Science and Medicine in the Old South,* ed. Ronald L. Numbers and Todd L. Savitt (Baton Rouge: Louisiana State University Press, 1989), 179–205.

45. W. D. Sutliff and Maxwell Finland, "Type I Lobar Pneumonia Treated with Concentrated Pneumococcic Antibody (Felton): The Clinical Course," *Journal of the American Medical Association* 96 (1931): 1465.

46. A. Nainka to Rufus Cole, 11/20/32 [RCP].

47. F. M. Huntoon, "Treatment of Pneumonia with Pneumococcus Antibody Solution," *Journal of the Medical Society of New Jersey* 25 (1928): 12.

48. G. R. Maxwell, "Pneumonia," *West Virginia Medical Journal* 29 (1933): 302, 303. Such a statement was made shortly after his advocating the use of digitalis "as soon as a diagnosis is made," despite the formal disproof of the utility of digitalis in treating pneumonia in a controlled clinical trial in 1930. See Wyckoff, Dubois, and Woodruff, "The Therapeutic Value of Digitalis in Pneumonia."

49. F. M. Wiley, "The Treatment of Lobar Pneumonia," *Journal of the Kansas Medical Society* 30 (1929): 213.

50. Julius Levy, in Huntoon, "Treatment of Pneumonia with Pneumococcus Antibody Solution," 12.

51. F. M. Huntoon, in ibid., 13.

52. Naomi Rogers, *Dirt and Disease: Polio Before FDR* (New Brunswick, N.J.: Rutgers University Press, 1992), 72–96.

53. F. C. Shattuck and C. H. Lawrence, "Acute Lobar Pneumonia," *Boston Medical and Surgical Journal* 178 (1918): 251.

54. Russell L. Cecil, "The Prevention and Serum Treatment of Lobar Pneumonia," *Medical Clinics of North America* 4 (1920): 191; Russell L. Cecil, "Specific Prevention and Specific Treatment of Lobar Pneumonia," *Military Surgeon* 53 (1923): 462.

55. L. L. Powell, "Treatment of Pneumonia Based upon Recent Clinical, Bacteriological, and Pathological Findings," *Journal of the Maine Medical Association* 10 (1920): 160.

56. Stewart R. Roberts, "The Treatment of Pneumonia," *Journal of the Medical Association of Georgia* 14 (1925): 114; See also D. Armstrong, "Respiratory Diseases," *Journal of the Oklahoma State Medical Association* 22 (1929): 1; O'Hara, "Pneumococcus Lobar Pneumonia," 223.

57. See, e.g., the opening lines of Cyrus W. Strickler, "A Comparison of the Different Plans of Managing the Patient Suffering with Pneumonia," *Southern Medicine and Surgery* 92 (1930): 228.

58. W. C. Todt, in James H. Allen, "The Treatment of Pneumonia," *Southwestern Medicine* 13 (1929): 348. Todt continued: "Thirty years ago I used carbonated water, and I still use it."

59. O. D. Sharpe, "Pneumonia: Its Management and Treatment from a General Practitioner's Standpoint," *Journal of the Kansas Medical Society* 24 (1924): 315.

60. Powell, "Treatment of Pneumonia Based upon Recent Clinical, Bacteriological, and Pathological Findings," 160.

61. Franklin C. McLean, "Lobar Pneumonia: Specific Etiology and Therapy," *Wisconsin Medical Journal* 28 (1929): 2.

62. "In fact there have been very few specifics discovered in all the history of medicine. We must of necessity depend largely upon the symptomatic treatment of diseases as has been the custom in the past (Albert H. Hoge, "A Rational Treatment of Pneumonia," *West Virginia Medical Journal* 19 [1924]: 10). Hoge, however, cited type I antipneumococcal antiserum as an exception to this historical rule.

63. Edward E. Cornwall, "A Primer on Pneumonia Therapeutics," *Medical Journal and Record* 133 (1931): 175; Harlow Brooks, "The Treatment of Pneumonia," *Medical Clinics of North America* 5 (1922): 999. See also McGrew, "A Rational Treatment of Pneumonia," 316; F. L. Rogers, in A. A. Conrad, "Treatment of Pneumonia," *Nebraska State Journal of Medicine* 16 (1931): 56.

64. "We all or rather most of us know and sadly remember how we have fallen for gold and silver mining stock and are still waiting for oil to spout to make us millionaires, fruit lands to reach $400 to $600 an acre, to take care of us in our old age, and so forth. Here, at least, we have not done any harm to our patients, but let us be careful not to use new remedies which may, to our chagrin, cost a life every now and then" (H. T. Nippert, "Treatment of Pneumonia," *Minnesota Medicine* 6 [1923]: 535). Regarding clinicians' contemporary concerns regarding commercialism in medicine, see Keith Wailoo, *Drawing Blood: Technology and Disease Identity in Twentieth-Century America* (Baltimore: Johns Hopkins University Press, 1997), 126.

65. See, for example, D. W. Fenton, "Prophylaxis and Treatment of Lobar Pneumonia," *Journal of the Michigan State Medical Society* 29 (1930): 371; C. A. McKinlay, "Treatment of Lobar Pneumonia," *Journal-Lancet* 53 (1934): 672.

66. Harlow Brooks, "The Treatment of Pneumonia," *Northwest Medicine* 22 (1923): 11. See also Harlow Brooks to Rufus Cole, 11/26/17 [RCP].

67. Brooks, "The Treatment of Pneumonia [1922]," 994.

68. Ibid., 1004. See also J. B. Pankau, "The Treatment of Pneumonia," *Nebraska State Medical Journal* 17 (1932): 28.

69. Brooks, "The Treatment of Pneumonia [1922]," 1006. For the nineteenth-century American basis of such gendering, initially between those who attempted to intervene upon, and those who attempted to rely upon, nature's own healing efforts, see Charles E. Rosenberg, *The Care of Strangers: The Rise of America's Hospital System* (New York: Basic Books, 1987), 133–34; 217–19; John Harley Warner, *Against the Spirit of the System: The*

French Impulse in Nineteenth-Century American Medicine (Princeton, N.J.: Princeton University Press, 1998), 286.

70. A. Elkin, in E. C. Thrash, "Treatment of Pneumonia," *Journal of the Medical Association of Georgia* 15 (1926): 90.

71. E. C. Thrash, in ibid., 91.

72. Joseph E. McClelland, "Determination of Type and Serum Treatment in Pneumococcus Infections," *Cleveland Medical Journal* 17 (1918): 227.

73. Jesse G. M. Bullowa, "Lobar Pneumonia Type II Treated with Felton and Banzhaf and Sobotka's Antibody Solution," *Medical Clinics of North America* 12 (1928): 704.

74. J. B. Graeser, "Rationale of Specific Therapy in Lobar Pneumonia," *Medical Clinics of North America* 16 (1932): 459.

75. Joel D. Howell, *Technology in the Hospital* (Baltimore: Johns Hopkins University Press), 198. With respect to blood counts, much of the change at both hospitals occurred between 1900 and 1910; with respect to chest x-rays, much of the change at the Pennsylvania Hospital took place between 1920 and 1925, while that at New York Hospital took place between 1910 and 1920.

76. Ibid., 207–16. See also Gerald L. Geison, "Divided We Stand: Physiologists and Clinicians in the American Context," in *The Therapeutic Revolution: Essays in the Social History of American Medicine,* ed. Morris J. Vogel and Charles E. Rosenberg (Philadelphia: University of Pennsylvania Press, 1979), 73–75; Russell C. Maulitz, "'Physician Versus Bacteriologist': The Ideology of Science in Clinical Medicine," in *The Therapeutic Revolution,* 91–107; Wailoo, *Drawing Blood,* especially 17–45.

77. S. L. Gabby, "Treatment of Pneumonia," *Illinois Medical Journal* 45 (1924): 367; Wiley, "The Treatment of Lobar Pneumonia," 215; H. T. Safford, "A Rational Treatment of Pneumonia (A Paper with a Message)," *Southwestern Medicine* 16 (1932): 77.

78. C. N. B. Camac, "Antipneumococcus Serum in Lobar Pneumonia. A Clinical Report," *American Journal of Medical Sciences* 166 (1923): 543. Camac, an Osler disciple, had himself edited a textbook of physical diagnosis in 1905. See John Metcalfe Polk, *Notes on Physical Diagnosis,* ed. C. N. B. Camac (New York: Cornell Medical College, 1905).

79. Brooks, "The Treatment of Pneumonia (1922)," 994–95. It is not surprising that Brooks subtitled his presentation, "Based on a Broad Clinical Experience and a Description of Measures which One Will Be Called Upon Most Frequently to Use; Knowledge Not Derived from the Laboratory Nor from the Dead-house, but from a Study of the Disease as it is Seen Clinically in the Ward and By the Bedside of the Private Patient."

80. Harry Dowling, who would come of medical age in the antiserum era under Finland's training, before emerging as a leading infectious disease expert and historian of medicine, had himself noted such persistent tensions in his diary in 1934 (at the age of thirty): "I have been thinking over the problem of laboratory work for the medical profession. There are two opposite views of thought on this question. One group thinks that laboratory work is a very unimportant diagnostic aid; that what we need is good clinicians, trained to make a good diagnosis on physical findings, calling in the aid of the laboratory (including x-ray and electrocardiographic findings) only in the few instances when an uncertain diagnosis on other bases prevents necessary treatment. The other school believes that the day of 'guessing' from clinical findings is past; and that the laboratory is coming

more and more to the front, and will soon displace all other types of diagnosis" [HDP, Box 1, Diary entry, 1/12/34].

81. Henry D. Chadwick, "Final Report of Massachusetts Pneumonia Study and Service," *Commonhealth* 24 (1937): 11.

82. See, for example, Rosenberg, *The Care of Strangers;* Rosemary Stevens, *In Sickness and in Wealth: American Hospitals in the Twentieth Century* (New York: Basic Books, 1989).

83. L. A. Nippert, "Prognosis and General Management of the Pneumonias," *Journal-Lancet* 41 (1921): 67–68.

84. S. M. White, in ibid., 69.

85. See J. F. Anderson, "Pneumonia and Some Practical Methods of Treatment," *Journal of the Medical Association of Georgia* 20 (1931): 131; C. C. Hall, "The Treatment of Pneumonia," *Journal of the Iowa State Medical Society* 22 (1932): 76.

86. Doctor Beecher, in Francis G. Blake, "The Diagnosis and Treatment of Pneumonia," *New England Journal of Medicine* 202 (1930): 994.

87. Russell L. Cecil, "Experience with Special Biologicals in the Treatment of Pneumonia," *Journal of the Medical Society of New Jersey* 26 (1929): 115.

88. Harold I. Reynolds, "Modern Management of Pneumonia: Report of Fourteen Cases," *Journal of the Medical Association of Georgia* 17 (1928): 203.

PART II. THE TRANSFORMATION OF PNEUMONIA INTO A PUBLIC HEALTH CONCERN, 1930–1939

1. For discussions regarding the formation, discussions, and consequences of the Committee on the Costs of Medical Care, as well as regarding the split among its members between those advocating for group practice and prepaid medical care, and those perceiving such suggestions as a dangerous bridge to compulsory health insurance, see Paul Starr, *The Social Transformation of American Medicine: The Rise of a Sovereign Profession and the Making of a Vast Industry* (New York: Basic Books, 1982), 261–66; Jonathan Engel, *Doctors and Reformers: Discussion and Debate over Health Policy, 1925–1950* (Columbia: University of South Carolina Press, 2002), 11–52.

2. Louis I. Dublin, "The Health of the People in a Year of Depression," *American Journal of Public Health* 22 (1932): 1132–33; Louis I. Dubin, "The Threatened Health Emergency and the N.[I].R.A. [Radio Broadcast, National Broadcasting Company, 10/9/33]," [LDP, Box 4, "American Public Health Association"]. See also Elizabeth Fee, "The Origins and Development of Public Health in the United States," in *Oxford Textbook of Public Health,* 3rd ed., Volume I: *The Scope of Public Health,* ed. Roger Detels, Walter W. Holland, James McEwen, and Gilbert S. Omenn (New York: Oxford University Press, 1997), 39; John Duffy, *The Sanitarians: A History of American Public Health* (Urbana: University of Illinois Press, 1992), 257–60. As relevant to efforts against malaria in the first half of the twentieth century, see Margaret Humphreys, *Malaria: Poverty, Race, and Public Health in the United States* (Baltimore: Johns Hopkins University Press, 2001), 83–87.

3. James G. Burrow, *A.M.A.: Voice of American Medicine* (Baltimore: Johns Hopkins Press, 1963), 191–204; Daniel S. Hirshfield, *The Lost Reform: The Campaign for Compulsory Health Insurance in the United States from 1932 to 1943* (Cambridge, Mass.: Harvard Uni-

versity Press, 1970); Starr, *Social Transformation of American Medicine,* 260–61, 270–79; Engel, *Doctors and Reformers,* 60–65.

4. For a general discussion of the increasingly firm resistance of the American Medical Association to governmental public health expansion in the post-Progressivist era, see John Duffy, "The American Medical Association and Public Health: From Support to Ambivalence," *Bulletin of the History of Medicine* 53 (1979): 19–22; Allan M. Brandt and Martha Gardner, "Antagonism and Accommodation: Interpreting the Relationship between Public Health and Medicine in the United States During the 20th Century," *American Journal of Public Health* 90 (2000): 707–11.

Chapter 4. The Massachusetts Experiment and New (York) Tensions

1. Maxwell Finland, "The Modern Treatment of Pneumonia," *American Journal of Nursing* 36 (1936): 25. By the early 1930s, researchers were likewise at last reporting consistent success with the treatment of type II pneumococcal pneumonia, though in many ways recapitulating the stuttering history of its type I predecessor, both entailing the post hoc reformulation of patient data to include only those treated early in the course of disease and illustrating the ongoing tensions between statistical and personal authority. See Horace S. Baldwin, "The Specific Therapy of Pneumococcus Type I and Type II Pneumonia," *American Journal of Medical Science* 181 (1931): 788; Russell L. Cecil and Norman Plummer, "Pneumococcus Type II Pneumonia: A Clinical and Bacteriological Study of One Thousand Cases, with Especial Reference to Serum Therapy," *Journal of the American Medical Association* 98 (1932): 783, 786.

2. Harry F. Dowling, "The Rapid Diagnosis and Serum Treatment of Lobar Pneumonia," *Medical Annals of the District of Columbia* 4 (1935): 68. Such "newspaper" testimonials would thereafter frequently be reported, e.g., in Lewellys F. Barker, "Pneumonia in Adults," *Journal of the Medical Society of New Jersey* 32 (1935): 28; Russell L. Cecil, "Effects of Very Early Serum Treatment in Pneumococcus Type I Pneumonia," *Journal of the American Medical Association* 108 (1937): 690; Robert Toubib, "Pneumonia—An Emergency," *Hygeia* 18 (1940): 50.

3. For a review of such efforts, see Benjamin White, *The Biology of the Pneumococcus* (New York: Commonwealth Fund, 1938), 119–32.

4. Robert Austrian, "The Quellung Reaction: A Neglected Microbiologic Technique," *Mount Sinai Medical Journal* 43 (1976): 699–706.

5. By the early 1930s, Neufeld had himself attempted to transform the quellung reaction into a clinical test, and Sabin's development of the technique had been facilitated by the Rockefeller Institute's Kenneth Goodner, who had visited Neufeld's lab in Berlin, much as Cole had two decades prior. See Austrian, "The Quellung Reaction"; Albert B. Sabin, "Immediate Pneumococcus Typing Directly from Sputum by the Neufeld Reaction," *Journal of the American Medical Association* 100 (1933): 1584–86. For contemporary developments of the technique in Great Britain, see Richard R. Armstrong, "Immediate Pneumococcal Typing," *British Medical Journal* 1(1932): 187–88; W. R. Logan and J. T. Smeall, "A Direct Method of Typing Pneumococci," *British Medical Journal* 1 (1932): 188–89.

6. Dowling, "The Rapid Diagnosis and Serum Treatment of Lobar Pneumonia," 66.

7. Over the ensuing years, such an ideal would continue to be promulgated by the Neufeld technique's advocates: "To have the experience of obtaining a good specimen of sputum from a patient, carrying out the typing on it oneself, and forthwith successfully administering appropriate serum with its dramatic effect constitutes a satisfaction unique in any physician's experience" (W. H. Potts, "Serum Therapy in Lobar Pneumonia," *Texas State Journal of Medicine* 33 [193]: 419). However, its characterization as such a simple procedure made the actual difficulties attendant on its application that much more frustrating. See Julien E. Benjamin, Marion Blankenhorn, James Ruegsegger, and Fannie Senior, "Study of the Diagnosis and Treatment of Lobar Pneumonia According to Types and Specific Serum Therapy," *Annals of Internal Medicine* 11 (1937): 437; James M. Ruegsegger, "A School for 'Typers,'" *Ohio State Medical Journal* 34 (1938): 188.

8. Milton Rosenau would declare her efforts "one of the outstanding pieces of work of the Metropolitan Influenza and Pneumonia Commission" (cited in R. L. Cecil, J. G. M. Bullowa, H. T. Chickering, and E. H. L. Corwin, "Community Provision for the Serum Treatment of Pneumococcic Pneumonias," *Journal of the American Medical Association* 109 [1937]: 1324).

9. Georgia Cooper, Marguerite Edwards, and Carolyn Rosenstein, "The Separation of Types among the Pneumococci Hitherto Called Group IV and the Development of Therapeutic Antiserums for these Types," *Journal of Experimental Medicine* 49 (1929): 461–74; Georgia Cooper, Carolyn Rosenstein, Annabel Walter, and Lenore Peizer, "The Further Separation of Types among the Pneumococci Hitherto Included in Group IV and the Development of Therapeutic Antisera for these Types," *Journal of Experimental Medicine* 55 (1932): 531–54. By 1995, ninety serotypes would be identified, a number that remains unchanged to this point. See Jørgen Henrichsen, "Six Newly Recognized Types of *Streptococcus pneumoniae*," *Journal of Clinical Microbiology* 33 (1995): 2759–62.

10. W. D. Sutliff and Maxwell Finland, "The Significance of the Newly Classified Types of Pneumococci in Disease: Types IV to XX Inclusive," *Journal of the American Medical Association* 101 (1933): 1289–95. They found the six most frequent types, in order, to be: I, II, III, VIII, V, and VII.

11. Finland, in discussion following, ibid., 1295.

12. Hobart A. Reimann, ibid., 1294. A Tennessee practitioner would concur three years later: "One may predict that it is only a matter of time until therapeutic antiserum will be available for each type, and we must be ready to avail ourselves of such remedies when placed at our disposal. The time is not far distant when it will be just as slipshod to make a diagnosis of pneumonia, without giving the type, as it now is to make a diagnosis of fever, without going further to determine whether it is a case of malarial fever, typhoid fever, or some other form of continued fever" (William R. Cate, "Pneumonia, with Special Reference to Typing and Specific Therapy," *Journal of the Tennessee Medical Association* 29 [1936]: 428).

13. Polyvalent serotherapy, with its justification undermined by the advent of such improved typing procedures and with its application undermined by the perceived difficulty of combining multiple types of antibodies into a single serum, would hence give way to monovalent (or, at most, bivalent or trivalent) antiserum buttressed by this ethos of specificity. See William H. Park, "The Types of Pneumococci in Adults and Children, and the Value of Specific Serum and Vaccine in the Treatment of Lobar Pneumonia," *Proceed-*

ings of the California Academy of Medicine 3 (1932–33): 69. The advent of Lederle Laboratories as a leading supplier and proponent of concentrated monovalent and bivalent antipneumococcal serotherapy at this time likewise appears to have contributed to the dissemination of such an ethos. While the *Bulletin of Lederle Laboratories,* begun in 1933, serves as a useful primary source, the absence of available Lederle archival records as a window into the era is unfortunate.

14. For clinicians respectively (if not respectfully) dismissing antiserum in terms of the (misrepresented) contemporary immunological literature, serum's apparent lack of efficacy in one's own hospital, and its ongoing impracticality (on account of serum's excessive specificity), see F. W. Harrell, in Morgan Smith, "Lobar Pneumonia," *New Orleans Medical and Surgical Journal* 89 (1936): 179; Edwin L. Bruck and Leo P. Guenther, in W. E. R. Schottstaedt, "Lobar Pneumonia: An Attempt to Evaluate Various Methods of Treatment," *California and Western Medicine* 41 (1934): 246, 247.

15. Oscar W. Bethea, "Treatment of Pneumonia," *Journal of the Kansas Medical Society* 35 (1934): 445.

16. "Bill" to Maxwell Finland, 11/25/34 [Series II, Subseries A, Box 5, Folder 28, MFP].

17. Leon H. Collins, "Specific Therapy, Oxygen Therapy and Symptomatic Treatment of Pneumonia," *Medical Clinics of North America* 19 (1935): 3; H. J. Moersch, "The Treatment of Pneumonia," *Proceedings of the Staff Meetings of the Mayo Clinic* 9 (1934): 187.

18. D. B. Armstrong, "Competitive Plagues of Mankind," *Better Health* 13 (1935): 304.

19. See Cyrus C. Sturgis, "An Appraisal of the Methods of Treating Pneumonia," *Journal of the Michigan State Medical Society* 34 (1935): 60; Harry Draper Jump, "The Use of Serum, Oxygen, and Artificial Pneumothorax in the Treatment of Pneumonia," *Delaware State Medical Journal* 7 (1935): 65–66; Alvin E. Price, "The Serum Treatment of Lobar Pneumonia: Report on the Use of Felton's Serum in Detroit from February 25 to June 1, 1935," *Journal of the Michigan State Medical Society* 34 (1935): 757.

20. William R. Cate, "Pneumonia, with Special Reference to Typing and Specific Therapy," 429.

21. J. L. Bibb, in ibid., 431.

22. See, for example, "Queries and Minor Notes: Treatment of Pneumonia at Home," *Journal of the American Medical Association* 102 (1934): 313; J. H. Meigs, "The Treatment of Pneumonia," *Journal of the Medical Association of Alabama* 5 (1936): 309.

23. The first equation of pneumonia with a surgical emergency "demanding as prompt action" appeared in the *British Medical Journal* in 1927 in a presentation on vaccine therapy. See W. H. Wynn, "II. The Vaccine Treatment of Acute Pneumonia," *British Medical Journal* 2 (1927): 481. See also Cyrus W. Strickler, "A Comparison of the Different Plans of Managing the Patient Suffering with Pneumonia," *Southern Medicine and Surgery* 92 (1930): 228; Rufus Cole, "The Treatment of Pneumonia," *Annals of Internal Medicine* 10 (1936): 3; E. F. Roberts, "Pneumococcus Pneumonia: With Special Reference to Type Diagnosis and Serum Therapy," *Journal of the Kansas Medical Society* 37 (1936): 282. Frederick T. Lord and Roderick Heffron, *Lobar Pneumonia and Serum Therapy, with Special Reference to the Massachusetts Pneumonia Study* (New York: Commonwealth Fund, 1936): 2.

24. W. B. Moody, "Serology of Pneumonia," *Nebraska State Medical Journal* 19 (1934): 58.

25. Indeed, at the community level, the comparison to diphtheria was again a loaded

one. When Lederle Laboratories commenced their company's *Bulletin* by citing William H. Park's declaration that "Type I antipneumococcic serum is almost as good as diphtheria antitoxin," they implicitly equated antipneumococcal antiserum with a modality itself initially funded through community efforts. See "The Treatment of Pneumonia with Antipneumococcic Serum," *Bulletin of Lederle Laboratories* 1 (1933): 1. For the public funding of diphtheria antitoxin in New York City in the 1890s, see Evelynn Maxine Hammonds, *Childhood's Deadly Scourge* (Baltimore: Johns Hopkins University Press, 1999), 88–119.

26. W. D. Sutliff and Maxwell Finland, "Type I Pneumococcic Infections with Especial Reference to Specific Serum Treatment," *New England Journal of Medicine* 210 (1934): 244.

27. Barbara Gutmann Rosenkrantz, *Public Health and the State: Changing Views in Massachusetts, 1842–1936* (Cambridge: Harvard University Press, 1972), 1.

28. Ibid., 97–127. Pneumonia, as a subject of concern, also remains largely absent from Rosenkrantz's text.

29. Ibid., 161. See also Louis I. Dublin to George H. Bigelow, 3/20/29; Louis I. Dublin, "Problem of Communicable Disease in Massachusetts [An Address on Health to the Statecraft Institute, Boston, 4/17/29]," [both in LDP, Box 12, "Problem of Communicable Diseases in Massachusetts"]; George H. Bigelow and Herbert L. Lombard, *Cancer and Other Chronic Diseases in Massachusetts* (Boston: Houghton Mifflin, 1933), 1–23. For the expansion of such an outlook to the federal level, see Hugh S. Cummings [Surgeon General, U.S. Public Health Service], "Chronic Disease as a Public Health Problem," *Vital Speeches of the Day* 2 (1936): 325–27.

30. For the year 1929, there were 2,561 recorded deaths from tuberculosis and 2,202 deaths from pneumonia, with an additional 1,185 recorded deaths from influenza. See Commonwealth of Massachusetts, *15th Annual Report of the Department of Public Health for the Year Ended November 30, 1929,* 61.

31. Roderick Heffron and Gaylord W. Anderson, "Two Years' Study of Lobar Pneumonia in Massachusetts," *Journal of the American Medical Association* 101 (1933): 1286.

32. Francis Blake to Rufus Cole, 11/22/18 [RCP].

33. Rosenkrantz, *Public Health and the State,* 112–15, 118–27.

34. Benjamin White to Barbara S. Quin, 5/11/37 [Box 249, Folder 2377, Series 18.1 (Grants), RAC]. Regarding White's scientific prominence as well as his critical influence on Oswald Avery himself prior to Avery's departure for the Rockefeller, see Robert Austrian, "Pneumococcus and the Brooklyn Connection," *American Journal of Medicine* 107 (1999): 3S-4S.

35. See Bernard W. Carey, "Lessons from a Study of One Thousand Diphtheria Deaths," *Boston Medical and Surgical Journal* 180 (1919): 67–70; Edward A. Lane and Filip C. Forsbeck, "Diphtheria Deaths in Massachusetts, 1926: Second Chronological Report," *New England Journal of Medicine* 198 (1928): 73–78; Edward A. Lane, "Diphtheria Deaths in Massachusetts, 1927: Third Chronological Report," *New England Journal of Medicine* 199 (1928): 939–44.

36. Benjamin White to Barbara S. Quin, 5/11/37 [Box 249, Folder 2377, Series 18.1 (Grants), RAC].

37. From 1928 through early 1931, 152 patients had been so treated. In George H. Bigelow, "The Serum Treatment of Pneumonia," *New England Journal of Medicine* 205 (1931): 244.

38. "Proposed Pneumonia Study and Service to be Undertaken by the Massachusetts Department of Public Health, 1930," 9/29/30, included with George H. Bigelow to Barbara S. Quin, 10/7/30 [Box 184, Folder 1728, Series 18.1 (Grants), RAC].

39. Bigelow, "The Serum Treatment of Pneumonia," 245.

40. Roderick Heffron, "Massachusetts Pneumonia Program," *New England Journal of Medicine* 206 (1932): 329. Such considerations were not by themselves novel. See J. Birney Guthrie, in Graham E. Henson, "Serum Therapy in Lobar Pneumonia, with Report of 67 Cases," *Southern Medical Journal* 13 (1920): 182. In 1926, moreover, Rufus Cole had written to Millard Knowlton, director of the Bureau of Preventable Diseases of the Connecticut Department of Health: "It now has been well demonstrated that the family physician is in the very best position to make effective use of antipneumococcus serum Type I in cases associated with Type I pneumococci. One of the chief reasons this serum has not proved more efficacious is that delays occur in administering it" (Rufus Cole to Millard Knowlton, 1/26/26 [RCP]).

41. Regarding the conference and its attendees, see Benjamin White to George H. Bigelow, 6/24/30 [Box 184, Folder 1728, Series 18.1 (Grants), RAC]; Elliott S. Robinson to Benjamin White, 5/25/37 [Box 249, Folder 2377, Series 18.1 (Grants), RAC]. Regarding the proposal, see Benjamin White to George H. Bigelow, 8/8/30 [Box 184, Folder 1728, Series 18.1 (Grants), RAC].

42. Bigelow, "The Serum Treatment of Pneumonia," 245. See also Benjamin White to George H. Bigelow, 8/8/30 [Box 184, Folder 1728, Series 18.1 (Grants), RAC].

43. See, e.g., Elizabeth Toon, "Selling the Public on Public Health: The Commonwealth and Milbank Health Demonstrations and the Meaning of Community Health Education," in *Philanthropic Foundations: New Scholarship, New Possibilities,* ed. Ellen Condliffe Lagemann (Bloomington: Indiana University Press, 1999), 120–21

44. George H. Bigelow to Barbara S. Quin, 12/22/30 [Box 184, Folder 1728, Series 18.1 (Grants), RAC]. Cf. with Bigelow, "The Serum Treatment of Pneumonia," 245.

45. Heffron, "A Study of Lobar Pneumonia in Massachusetts: Preliminary Report," *New England Journal of Medicine* 207 (1932): 155; Henry D. Chadwick, "Foreword to the Final Report of Massachusetts Pneumonia Study and Service," *Commonhealth* 24 (1937): 4. This published report, written by Heffron, differed only in rare instances from the "Final Report of Massachusetts Study and Service" submitted to the Commonwealth Fund on 2/27/36 [Box 184, Folder 1735, Series 18.1 (Grants), RAC].

46. George H. Bigelow to Barbara S. Quin, 8/22/32 [Box 184, Folder 1729, Series 18.1 (Grants), RAC]. See also W. G. Smillie, in Augustus B. Wadsworth, "Serum Therapy: Its Value in Pneumonia, Meningitis, Scarlet Fever and Other Streptococcus Infections," *Journal of the American Medical Association* 99 (1932): 208.

47. George H. Bigelow, "Progress Report on Lobar Pneumonia Service Study," submitted with George H. Bigelow to Barbara S. Quin, 10/24/31[Box 184, Folder 1728, Series 18.1 (Grants), RAC]. Bigelow continued by attempting to generalize to the potential control of other diseases as well: "If we are successful, real progress in control of deaths, and perhaps cases, will have been made and we will have developed a technique for decentralization of service which may have application to other diseases."

48. Bigelow, "The Treatment of Pneumonia," 246.

49. Heffron, "A Study of Lobar Pneumonia in Massachusetts," 155.

50. Roderick Heffron, "Final Report of Massachusetts Pneumonia Study and Service," *Commonhealth* 24 (1937): 25. See also "The Massachusetts Pneumonia Program: A Report to the Commonwealth Fund of Eighteen Months' Progress," mailed "under separate cover" from George H. Bigelow to Barbara S. Quin, 8/22/32, and received 8/24/32 [Box 184, Folder 1729, Series 18.1 (Grants), RAC]. By November of 1931 one intensive course, four town meetings, and a presentation before a single district medical society had been given. In "Resume of Work Accomplished by the Massachusetts Pneumonia Study and Service," accompanying George H. Bigelow to Barbara S. Quin, 11/5/31 [Box 184, Folder 1728, Series 18.1 (Grants), RAC]. By 1935, three intensive courses and symposia in twenty-four individual towns and before thirteen district medical societies had been given. See Heffron, "Final Report," 25–29. Regarding the development of "public health education" in the 1920s, see Toon, "Selling the Public on Public Health," 121–22.

51. By the end of 1933, over half the state's population would be geographically covered by the program. In "The Massachusetts Pneumonia Program: A Report to the Commonwealth Fund of Approximately Three Year's [*sic*] Work," accompanying Henry D. Chadwick to Barbara S. Quin, 10/13/33 [Box 184, Folder 1731, Series 18.1 (Grants), RAC].

52. Whereas 127 vials of concentrated serum had been dispensed in 1928, 691 had been dispensed in 1929, 1253 in 1930, 1392 in 1931, and 2111 through October of 1932. In " Supplementary Report of the Massachusetts Pneumonia Program to the Commonwealth Fund," accompanying George H. Bigelow to Barbara S. Quin, 11/2/32 [Box 184, Folder 1729, Series 18.1 (Grants), RAC].

53. Ibid. Cf. the last sentence with Bigelow's initial assertion of the "demand for the product" in 1930.

54. Heffron and Anderson, "Two Years' Study of Lobar Pneumonia in Massachusetts," 1288. Earlier, Heffron had written to the Commonwealth Fund administrators: "Up to the present—some 15 years later—no one else has ever been able to duplicate [Cole's] excellent results, and the current attitude of physicians at large is that it can not be done. We believe it can be done" ("Supplementary Report of the Massachusetts Pneumonia Program to the Commonwealth Fund," [Box 184, Folder 1729, Series 18.1 (Grants), RAC]).

55. In "The Massachusetts Pneumonia Program: A Report to the Commonwealth Fund of Approximately Three Year's Work" [Box 184, Folder 1731, Series 18.1 (Grants), RAC].

56. Compare George H. Bigelow to Barbara S. Quin, 10/16/30, with George H. Bigelow to Barbara Quin, 12/22/30 [both in Box 184, Folder 1728, Series 18.1 (Grants), RAC]. Explained Bigelow in the latter letter: "The whole service is aimed at giving effective aid to such practitioners" in the first place.

57. Frederick Lord, in Heffron, "A Study of Lobar Pneumonia in Massachusetts," 157.

58. Heffron, "Massachusetts Pneumonia Program," 329.

59. Heffron, missing the larger point, would summarize: "There have been some criticisms of this plan—chiefly on a financial basis. We feel that when a doctor gives four or five hours of a day or night to treat a patient with serum, he should have a certain amount of financial return for the time expended" (ibid., 329).

60. For a contemporary lament concerning the difficulties of medical practice amidst the Depression, see Harry Heimann to Maxwell Finland, 11/13/32 [Series II, Subseries A,

Box 2, Folder 42, MFP]. See also *Medical Care for the American People: The Final Report of the Committee on the Costs of Medical Care* (Chicago: University of Chicago Press, 1932), 22–24; Ray Lyman Wilbur, "The Economics of Public Health and Medical Care," *Milbank Memorial Fund Quarterly* 10 (1932): 182; Jonathan Engel, *Doctors and Reformers: Discussion and Debate over Health Policy, 1925–1950* (Columbia: University of South Carolina Press, 2002), 26.

61. Heffron and Anderson, "Two Years' Study of Lobar Pneumonia in Massachusetts," 1286.

62. In "Supplementary Report of the Massachusetts Pneumonia Program to the Commonwealth Fund," [Box 184, Folder 1729, Series 18.1 (Grants), RAC].

63. Heffron, "Massachusetts Pneumonia Program," 329. Edwin Locke, speaking before the state medical society, concurred: "What the State Department of Health is trying to do is not to usurp the function of the practitioner and treat pneumonia, but rather to place in his hands the equipment which makes it possible for him to use effectively this new method of treating pneumonia" (in Heffron, "A Study of Lobar Pneumonia in Massachusetts," 157).

64. Ibid.

65. Barbara S. Quin, "Memorandum, Pneumonia Project—Conference with Dr. George H. Bigelow, Commissioner, Department of Public Health," 8/16/33 [Box 184, Folder 1730, Series 18.1 (Grants), RAC].

66. Regarding the Commonwealth Fund's request, see Barbara S. Quin to Roderick Heffron, 9/6/33 [Box 184, Folder 1730, Series 18.1 (Grants), RAC].

67. Heffron, "A Study of Lobar Pneumonia in Massachusetts," 156.

68. Heffron, "Final Report of Massachusetts Pneumonia Study and Service," 51. The unpublished final report sent to the Commonwealth Fund also noted: "Some jealousy was stirred up, for on the surface it appeared that this department regarded some physicians as more capable than others. . . . In a few areas an even more judicious selection of collaborators might have yielded still better results" ("Final Report of Massachusetts Pneumonia Study and Service," 60, 64 [Box 184, Folder 1735, Series 18.1 (Grants), RAC]).

69. Heffron, "Final Report of Massachusetts Pneumonia Study and Service," 52.

70. "Plan of Pneumonia Study for 1934 and 1935," accompanying Henry D. Chadwick to Barbara S. Quin, 10/13/33 [Box 184, Folder 1731, Series 18.1 (Grants), RAC].

71. Ibid.

72. It was noted that "should a physician desire serum for treatment of any other case, he would, of course, be able to purchase it as he would any other drug" (ibid.).

73. For physicians' willingness "to accept the restrictions of typing and early use of serum," and its being "regarded as an important finding" in its own right, see "The Massachusetts Pneumonia Program: Progress Report to the Commonwealth Fund," 10/17/34; see also Henry D. Chadwick to Barbara S. Quin, 10/11/34 [both in Box 184, Folder 1733, Series 18.1 (Grants), RAC]. The dissolution of the collaborator system occurred slowly, however: fees paid to the collaborators ran to $75.84 in 1931, $1,465.77 in 1932, $1,727.74 in 1933, $2,003.22 in 1934, and $1,032.12 in 1935 (Heffron, "Final Report of Massachusetts Pneumonia Study and Service," 51). In a telling alternative proposition, by 1935 it would instead be suggested: "In view of the fact that difficult questions regarding the treatment of

patients often arise, [Frederick Lord] also feels that there should be available in each part of the State some individual officially appointed by the district medical society to whom physicians could turn for a discussion of their case" (in Roderick Heffron to Lester J. Evans, 4/16/35; see also Lester J. Evans to Barbara S. Quin, 4/19/35 [both in Box 249, Folder 2374, Series 18.1 (Grants), RAC]).

74. Heffron, "Final Report of Massachusetts Pneumonia Study and Service," 39.

75. Ibid., 40.

76. When confronted with less comforting type II data showing a 27.2 percent mortality rate among the treated groups and a 21.6 percent mortality rate among "controls," Heffron would explain away the control group as a nonrepresentative sample, instead comparing the mortality rate among the treated patients with the traditionally cited figure of 41 percent. For Heffron, the control group's apparent low mortality was the result of what would have later been termed "reporting bias," given that most type II fatalities occurred early in the course of the disease, leaving only the less fulminant cases to be reported to health authorities. See Roderick Heffron to Barry C. Smith, 1/30/36; see also Roderick Heffron to Edward S. Rogers, 1/30/36 [both in Box 249, Folder 2375, Series 18.1 (Grants), RAC]. Indeed, a "few moments" before writing to Smith, Heffron had apparently telephoned Maxwell Finland to ascertain Boston City Hospital's untreated type II mortality rate and was quoted a figure of 51 percent over the preceding six years (in Roderick Heffron to Barry C. Smith, 1/30/36; Roderick Heffron to Edward S. Rogers, 1/30/36 [both in Box 249, Folder 2375, Series 18.1 (Grants), RAC]).

77. Roderick Heffron, "The Campaign Against Pneumonia," *New England Journal of Medicine* 214 (1936): 223.

78. See, e.g., Edith MacBride Dexter and Edward L. Bortz, "Pneumonia Control: A Plan for Pennsylvania," *Pennsylvania Medical Journal* 41 (1938): 280.

79. D. A. MacGregor, "Recent Advances in the Treatment of Pneumonia," *West Virginia Medical Journal* 34 (1938): 491.

80. For the origins of the term, see George H. Ramsey to Barbara S. Quinn [*sic*], 9/10/35, as well as the accompanying "Proposal for a Pneumonia Control Program in New York State" [Box 249, Folder 2374, Series 18.1 (Grants), RAC]. For the earliest and most glowing assessment of the New York state program—as well as of its impact on the expansion of the state laboratories themselves—see Anna M. Sexton, *A Chronicle of the Division of Laboratories and Research, New York State Department of Health: The First Fifty Years, 1914–1964* (Lunenberg, Vermont: Stinehour Press, 1967), 125–41. For a far less sanguine assessment of the program's accomplishments, see Harry M. Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (New York: Cambridge University Press, 1997), 65–67.

81. The divergence between the Rockefeller researchers and Met Life's Pneumonia Commission, for instance, continued to revolve around their respective support of unconcentrated serum (defended by the Rockefeller) versus concentrated serum (defended by Met Life).

82. A final source of funding for efforts to treat pneumonia during this era derived from Lucius Littauer, a philanthropist who had lost his wife to pneumonia in 1924 and who had reportedly spent over $120,000 by 1937 to help fund many of the New York studies.

Bullowa credited Littauer with funding the development of Sabin's slide technique as well as the development and proof of efficacy of type II serum "after the efficacy of this serum had been denied by Dr. Cole" (Jesse Bullowa to Louis Dublin, undated, though likely summer 1937 [LDP, Box 16, "Pneumonia"]). See also Russell L. Cecil, Jesse G. M. Bullowa, Henry T. Chickering, and E. H. L. Corwin, "Community Provision for the Serum Treatment of Pneumococcic Pneumonias," *Journal of the American Medical Association* 109 (1937): 1324; dedication page and preface to Jesse G .M. Bullowa, *The Management of the Pneumonias* (New York: Oxford University Press, 1937). Littauer himself kept a scrapbook of antipneumococcal victories [Box 17, Folder 156, LLP].

83. Thomas Parran, "Proposal for a Campaign for the Prevention of Mortality from Pneumonia in New York State," 6/25/35 [Box 249, Folder 2374, Series 18.1 (Grants), RAC]; Sexton, *A Chronicle of the Division of Laboratories and Research,* 66–69.

84. See Barbara S. Quin to Roderick Heffron, 12/16/31; Roderick Heffron to Barbara S. Quin, 12/17/31 [both in Box 184, Folder 1728, Series 18.1 (Grants), RAC].

85. "Proposal for a Pneumonia Control Program in New York State," 9/10/35 [Box 249, Folder 2374, Series 18.1 (Grants), RAC]. Parran, who would eventually play a central role in antipneumococcal serotherapy's attainment of national prominence, had been trained as a physician and served in the public health service since 1917 (rising to assistant surgeon general in 1926, heading the Division of Venereal Disease), before being chosen by then-Governor Franklin D. Roosevelt to head New York's state health department in 1930. See Ralph Chester Williams, *The United States Public Health Service, 1798–1950* (Washington, D.C.: Commissioned Officers Association of the United States Public Health Service, 1951), 484–85.

86. Peter Irving, "A State Medical Association's Part in a Pneumonia Control Program," *Journal of the American Medical Association* 110 (1938): 86B.

87. Regarding the state labs, see Mary Kirkbride to Thomas Parran, 2/4/35 [TPP, Box 16, FF 147], wherein Kirkbride had explained: "For the past six years the publicity rising from the pneumonia work supported by Mr. Littauer and the Metropolitan Life has doubtless accounted for the demands made upon us by many physicians and institutions as, for example, the Albany Hospital through Peter Ordway, the Dean of the Medical School, who has stressed both the prohibitive cost of the commercial concentrated serum and the pressure brought by physicians on the hospital for this treatment of their patients." Regarding the state medical society, see "Memorandum, Preliminary Discussion on New Pneumonia Program, Interview with Dr. Thomas Parran Jr., Commissioner, State Department of Health, New York," 5/1/35 [Box 249, Folder 2374, Series 18.1 (Grants), RAC].

88. See Thomas Parran to Herbert H. Lehman, 2/6/35; Thomas P. Farmer to Herbert H. Lehman, 2/13/35 [both in TPP, Box 16, FF 147]. Regarding the relationship between Parran and Lehman, see Thomas Parran to Herbert H. Lehman, 11/20/34 [TPP, Box 3, FF 14].

89. See Donald B. Armstrong to Thomas Parran, 4/18/35 [TPP, Box 16, FF 147]. Contrast this account with "Memorandum, Preliminary Discussion on New Pneumonia Program: Telephone Conversation with Dr. Thomas Parran Jr., Commissioner, State Department of Health, New York," 5/17/35 [Box 249, Folder 2374, Series 18.1 (Grants), RAC].

90. See Thomas Parran to Drs. Paul Brooks, Edward Godfrey, Augustus Wadsworth, and George Ramsey, 5/7/35; Augustus Wadsworth to Thomas Parran, 5/15/35 [both in TPP, Box 16, FF 147].

91. Not surprisingly, the twelve-member advisory committee consisted of six state medical society members (including Cecil), in addition to Rufus Cole from the Rockefeller, Donald Armstrong from Met Life, Clarence Scamman from the Commonwealth Fund, Arthur Wright from the New York Association of Public Health Labs, and Augustus Wadsworth and George Ramsey from the Department of Health. See "Pneumonia Control Program" (listing of members of the Advisory Committee of the New York Pneumonia Control Program), undated, though likely late 1935, early 1936 [TPP, Box 16, FF 147].

92. "Memorandum, Preliminary Discussion on New Pneumonia Program, Interview with Dr. Thomas Parran Jr., Commissioner, State Department of Health, New York," 5/1/35 [Box 249, Folder 2374, Series 18.1 (Grants), RAC].

93. Lehman would "proclaim the period from January 15 to February 15, 1936, as a season for all citizens to join in a common effort to reduce the number of pneumonia cases and deaths by disseminating knowledge of prevention through simple health rules and by prompt action in securing diagnosis and treatment where pneumonia is suspected" (Sexton, *A Chronicle of the Division of Laboratories and Research,* 127; see also in TPP, Box 16, FF 146).

94. "Text of a Radio Discussion Participated in by Governor Lehman, Doctor Frederic E. Sondern, President of the Medical Society of the State of New York, and Doctor Thomas Parran Jr., State Commissioner of Health, Opening the Campaign for Pneumonia Control in the State of New York and Broadcast from the Executive Mansion Over W.G.Y., January 14, 1936, 6:45 P.M.–7:00 P.M." [TPP, Box 16, FF 146]. Three years later, as surgeon general of the U.S. Public Health System, Parran would continue such a mantra, contrasting the dramatic public response to epidemic disease with the general laissez-faire attitude toward prevalent endemic diseases: "Though more than a hundred thousand persons die from the pneumonias every year, it does not seem a major disaster; because, in modern life, we seldom take personal responsibility for the sickness or misfortune of our neighbor" ("Health Needs of the Nation," *Public Health Reports* 54 [1939]: 920).

95. "Text of a Radio Discussion" [TPP, Box 16, FF 146].

96. Ibid.

97. George H. Ramsey, "Report on Pneumonia Control Program of the New York State Department of Health, November 1, 1935 to July 31, 1936," 8/15/36 [Box 249, Folder 2376, Series 18.1 (Grants), RAC].

98. State of New York, *58th Annual Report of the Department of Health for the Year Ending December 31, 1937,* 1:14.

99. Regarding the resultant logistical strains placed on the Division of Laboratories and Research, see Sexton, *A Chronicle of the Division of Laboratories and Research,* 128.

100. George Ramsey to Barbara S. Quin, 9/10/35 [Box 249, Folder 2374, Series 18.1 (Grants), RAC]. Earlier they had noted that the State Medical Society "may want to run the show itself, and that Cecil, in particular, may have ambitions in that direction." See "Memorandum, Preliminary Discussion on New Pneumonia Program, Interview with Dr. Thomas Parran Jr., Commissioner, State Department of Health, New York," 5/1/35 [Box 249, Folder 2374, Series 18.1 (Grants), RAC]. For the validity of such concerns, see Thomas Farmer to Thomas Parran, 10/15/35 [TPP, Box 16, FF 147].

101. See Floyd S. Winslow, "We Do Not Want Security: The Doctor's Obligation," *Vital Speeches of the Day* 2 (1936): 823.

102. Peter Irving, "A State Medical Association's Part in a Pneumonia Control Program," 86B.

103. See especially, Engel, *Doctors and Reformers,* 60–65, 108–13.

104. Winslow, "We Do Not Want Security," 822.

105. Ibid., 823.

106. Ibid.

107. Franklin Delano Roosevelt, who had initially "stolen" Parran from the public health service to place him as commissioner of New York's State Department of Health, claimed a "double steal" in returning Parran to the national service as its head. See Franklin Delano Roosevelt to Thomas Parran, 1/15/36 [TPP, Box 4, FF 28].

108. Concerning the difficulties encountered by the assistant state commissioner of health in obtaining physician compliance with the Fund's expectations regarding typing and the timing of serum distribution, see Barbara S. Quin, "New York State Pneumonia Program: Interview with George H. Ramsey, Assistant Commissioner, State Department of Health," 4/20/36 [Box 249, Folder 2375, Series 18.1 (Grants), RAC].

109. "Meeting of the Advisory Committee on Pneumonia Control of the New York State Department of Health," 12/20/35 [Box 249, Folder 2374, Series 18.1 (Grants), RAC].

110. Clarence Scamman to Barbara S. Quin, 3/14/36. See also Barbara S. Quin, "New York State Pneumonia Program: Interview with George H. Ramsey, Assistant Commissioner, State Department of Health," 4/20/36 [both in Box 249, Folder 2375, Series 18.1 (Grants), RAC].

111. Clarence Scamman, "Report of Attendance at New York State Pneumonia Committee Meeting at Saratoga Springs," 6/23/36 [Box 249, Folder 2375, Series 18.1 (Grants), RAC].

112. George H. Ramsey to Barbara S. Quin, 9/24/36 [Box 249, Folder 2376, Series 18.1 (Grants), RAC].

113. George H. Ramsey, "Report on Pneumonia Control Program of the New York State Department of Health," 8/15/36 [Box 249, Folder 2376, Series 18.1 (Grants), RAC].

114. The Fund's general director, Barry Smith, would expressly reject Ramsey's above-cited apologia for the state's coddling of its practitioners; see Barry C. Smith to George Ramsey, 9/25/36 [Box 249, Folder 2376, Series 18.1 (Grants), RAC].

115. Barbara S. Quin to Edward S. Godfrey, 9/21/36 [Box 249, Folder 2376, Series 18.1 (Grants), RAC]. Several years later, in funding pneumonia control on a county basis in Tennessee, the Commonwealth Fund administrators would again engender resentment (through their refusal to fund the provision of sulfa drugs, as opposed to serum) among physicians expecting more autonomy in therapeutic decision making. See W. C. Williams to Clarence Scamman, 8/25/39 [Box 36, Folder 520, Series 12.2, RAC].

116. "Interview with Dr. Ramsey," 8/19/37; Edward S. Godfrey to Barbara S. Quin, 9/23/37 [both in Box 249, Folder 2377, Series 18.1 (Grants), RAC]

117. See Irving, "A State Medical Association's Part in a Pneumonia Control Program," 87B; Sexton, *A Chronicle of the Division of Laboratories and Research,* 128.

118. For one exception, a pneumonia control program was instituted in 1937 in the District of Columbia with two "coordinators" (Harry Dowling and Theodore Abernathy) serving a function equivalent to the former Massachusetts collaborators. In such an instance,

the public health department offered the apologia that "there will be no disposition to displace the private physician" (Sterling Ruffin, "The Pneumonia Control Program of the District of Columbia," *Medical Annals of the District of Columbia* 7 [1938]: 383). For a parallel experience pertaining to Canadian cancer programs from the same era, see Charles R. R. Hayter, "Seeds of Discord: The Politics of Radon Therapy in Canada in the 1930s," *Bulletin of the History of Medicine* 77 (2003): 75–102.

Chapter 5. The New Standard, the New Deal, and the Pneumonia Control Programs

1. E. L. Bortz, in Norman Plummer, "The Use of Serum in the Treatment of the Higher Types of Pneumonia," *Journal of the American Medical Association* 111 (1938): 698. Bortz was referring in particular to the treatment of types I and II pneumococcal pneumonia but would later extend his confidence to several other types. By the late 1930s, several large series had demonstrated that from a quarter to a third of pneumococcal lobar pneumonia cases represented type I infection, that more than a tenth represented types II and III individually, and that the remainder represented the "higher types." Summarized in Roderick Heffron, *Pneumonia: With Special Reference to Pneumococcus Lobar Pneumonia* (Cambridge: Commonwealth Fund, 1939), 49–54.

2. Russell L. Cecil, "Effects of Very Early Serum Treatment in Pneumococcus Type I Pneumonia," *Journal of the American Medical Association* 108 (1937): 689. In more measured fashion, Marion Blankenhorn, reviewing 184 journal articles published from January of 1937 through June of 1938, found a unanimous advocacy of serum usage in treating type I or II pneumococcal pneumonia ("The Present Status of the Serum Therapy of Lobar Pneumonia," *Journal of the American Medical Association* 111 [1938]: 1260).

3. Cecil, "Effects of Very Early Serum Treatment," 691. Forgiving my presentist analysis of his study, Cecil might be accused of retrospective selection bias in making such a claim as he culled the cases from his own records and from those of such colleagues as Roderick Heffron, Edward Rogers, and Jesse Bullowa (whose "study," in this instance, had been reported in the *Bulletin of Lederle Laboratories!*). See "The Hospital Management of the Pneumonias," *Bulletin of Lederle Laboratories* 3 (1935): 10. Bullowa's name was not actually appended to the article but was cited as such by Cecil.

4. Declared Cecil: "The disease may be completely aborted" ("Effects of Very Early Serum Treatment," 692).

5. Julien E. Benjamin, Marion Blankenhorn, and Fannie A. Senior, "The Results of the Treatment of Pneumonia with Specific Therapeutic Serum," *Ohio State Medical Journal* 33 (1937): 39. Again, such a finding would today be considered the outcome of a post hoc subgroup analysis, based on the convenient defining of "early" as within ninety-six hours of disease onset and of "adequate" as with 40,000 units of serum or more.

6. See Marion A. Blankenhorn, "The Present Status of the Serum Therapy of Lobar Pneumonia," 1261; Angelo L. Luchi, "The General Practitioner and the 1938 Pneumonia Control Campaign," *Pennsylvania Medical Journal* 42 (1939): 510.

7. Jesse G. M. Bullowa, "Pneumonias: Their Management," *California and Western Medicine* 46 (1937): 370.

8. See J. D. Dowling and George A. Denison, "Lobar Pneumonia: Etiologic Diagnosis and Specific Treatment," *Journal of the Medical Association of Alabama* 7 (1937): 213; Plummer, "The Use of Serum in the Treatment of the Higher Types of Pneumonia," 697; Edith MacBridge-Dexter and Edward L. Bortz, "Pneumonia Control: A Plan for Pennsylvania," *Pennsylvania Medical Journal* 41 (1938): 280.

9. Regarding Lederle's efforts in this respect, see Jesse G. M. Bullowa, "Discussion on the Prophylaxis and Serum Treatment of Pneumonia," in *Report of Proceedings, Second International Congress for Microbiology,* ed. R. St. John-Brooks (London: International Society for Microbiology, 1937), 503; "The Use of the Rabbit in the Production of Antipneumococcic Sera for the Treatment of Pneumonia," *Bulletin of Lederle Laboratories* 5 (October 1937): 82–84.

10. F. L. Horsfall Jr., Kenneth Goodner, C. M. MacLeod, and A. H. Harris 2nd, "Antipneumococcus Rabbit Serum as a Therapeutic Agent in Lobar Pneumonia," *Journal of the American Medical Association* 108 (1937): 1487.

11. Frank L. Horsfall Jr., Kenneth Goodner, and Colin M. Macleod, "Antipneumococcus Rabbit Serum as a Therapeutic Agent in Lobar Pneumonia. II: Additional Observations in Pneumococcus Pneumonias of Nine Different Types," *New York State Journal of Medicine* 38 (1938): 255. Regarding the NIH's own enthusiasm for the remedy, see W. T. Harrison, chief of the Division of Biological Control, "Memorandum for the Director, National Institutes of Health," 7/8/38 [RG443 0425, Box 14].

12. Outside the United States, antipneumococcal serotherapy was perhaps most widely hailed and applied in Denmark, which had its own strong serological tradition. Wrote the Rockefeller's Frank Horsfall Jr. to Rufus Cole in mid-1938: "Beginning last September, Dr. [Thorvald] Madsen [of the Statens Serum Institut in Copenhagen] set out to produce rabbit serum for the whole of Denmark. . . . Cleaned and disinfected all his old horse stables, and filled the stalls with rabbit cases. He then commenced breeding his own rabbits, brought in five full time assistants (M.D.'s) and fifteen technicians not to mention a whole colony of animal men etc. He has sera against all thirty [*sic*] types. . . . When I say all thirty, I mean also that he actually has potent type III antisera. This I heard and definitely didn't quite believe, but it is true. There are now some 3,000 rabbits under active immunization, and the breeding colony contains an additional 10,000 (!) which will soon be ready to include in the immunized group. . . . The bottled sera is perfectly clear, as colorless as ours, sterile, and does not produce chills! . . . They told me that in a group of 200 cases, treated within the first three days, there wasn't a single death. This group includes many types, even III. . . . They are stressing early diagnosis, early serum, and lots of it just as you have for so many years. . . . It will be, I think, exceedingly interesting to follow the results obtained in this small and beautifully organized country during the next few years" (Horsfall Jr. to Cole, 6/13/38 [RCP]).

13. See J. D. Gray and M. C. Fulton, "The Mortality and Treatment of Lobar Pneumonia," *Journal of the Medical Association of Georgia* 27 (1938): 420; Russell L. Cecil, "Present Status of Serum Therapy in Pneumonia," *Bulletin of the New York Academy of Medicine* 15 (1939): 110.

14. See W. H. Potts, "Serum Therapy in Lobar Pneumonia," *Texas State Journal of Medicine* 33 (1937): 418; W. D. Sutliff, "Type-Specific Anti-Pneumococcic Serum Therapy," *Illi-*

nois Medical Journal 72 (1937): 512; Sterling Ruffin, "The Pneumonia Control Program of the District of Columbia," *Medical Annals of the District of Columbia* 7 (1938): 381; Arthur W. Burnham, in Frederick T. Lord, "Pneumococcus Pneumonia," *New England Journal of Medicine* 219 (1938): 487.

15. Potts, "Serum Therapy in Lobar Pneumonia," 418; see also D. A. MacGregor, "Recent Advances in the Treatment of Pneumonia," *West Virginia Medical Journal* 34 (1938): 485.

16. Potts, "Serum Therapy in Lobar Pneumonia," 418.

17. Peter Irving, "Reduction of Mortality from Pneumococcus Pneumonia," *Preventive Medicine* 7 (1938): 16.

18. MacGregor, "Recent Advances in the Treatment of Pneumonia," 485.

19. See Oscar W. Bethea, "Present Status of the Treatment of Pneumonia," *Journal of the Medical Association of Alabama* 8 (1938): 143–44; Wyndham B. Blanton, in Douglas G. Chapman, "Diagnosis and Treatment of Lobar Pneumonia," *Virginia Medical Monthly* 66 (1939): 136.

20. Harold D. Levine, "The Opportunity for the Modern Treatment of Lobar Pneumonia in General Practice," *New England Journal of Medicine* 219 (1938): 644. Increasingly, such symptomatic care was to be deemed insufficient in and of itself for the treatment of the sick patient. In response to a statement by Louis Dublin (in the rough draft sent to Bullowa of an article concerning pneumonia for *Colliers*) that "even before the newer therapy became known, many physicians had developed real skill in carrying their cases through successfully," Jesse Bullowa had replied: "I think the paragraph referring to the real skill of physicians in carrying their cases through successfully is superfluous, misleading, and untrue. I know of no method other than serum at the present time by which a physician can successfully treat a patient suffering from bacteremia. Non-bacteremic cases usually get better regardless of medical skills" (Jesse Bullowa to Louis Dublin, undated, though likely summer 1937 [LDP, Box 16, "Pneumonia"].

21. J. H. Musser and M. J. Boggs, "A Pregnant Woman with Lobar Pneumonia, Type VIII, Cured by Specific Serum [along with subsequent editorial]," *New Orleans Medical and Surgical Journal* 91 (1938): 246, 249–50; Samuel Ainslie Shelburne, in Moise D. Levy, "Modern Trends in the Diagnosis and Medical Treatment of Lobar Pneumonia," *Texas State Journal of Medicine* 33 (1937): 418; Byron F. Francis, in Plummer, "The Use of Serum in the Treatment of the Higher Types of Pneumonia," 698–99. However, for the persistence of impressionism, cf. Philip G. Corliss, in ibid., 699.

22. After a presentation before the California Medical Association of a study of the use of potassium permanganate in treating pneumonia, a discussant offered: "This study reminds one that there are a great many more problems to be investigated than there are investigators. Perhaps it would be helpful if the American Medical Association were to have a department on research to coordinate the various workers, and to foster research by supplying problems to those desiring them. For example, in the investigation of the various newer therapeutic measures used in pneumonia, workers in each hospital desiring to carry on research could be supplied with separate problems. Cases of control and those subjected to the treatment under investigation should alternate for more reliable results. If several methods are being studied, the cases should be taken in rotation" (Leo P. Guenther, in

W. E. R. Schottstaedt, "Lobar Pneumonia: An Attempt to Evaluate Various Methods of Treatment," *California and Western Medicine* 41 [1934]: 246). Guenther would be followed by William Kerr, who five years later, in response to a query from the FDA regarding the potential release of sulfapyridine, would suggest: "Perhaps qualified clinicians in many centers could be designated for clinical control as an intermediate step although I know the criticism this might cause among the profession" (William J. Kerr to W. G. Campbell, 2/8/39 [NDA, Vol. III]).

23. C. P. Jones Jr., "Serum Treatment of Pneumonia," *Virginia Medical Monthly* 65 (1938): 628.

24. For the advocacy of home treatment, see Arthur L. Smith, "Results of Treatment in Lobar Pneumonia," *Nebraska State Journal of Medicine* 22 (1937): 179. For that of hospital treatment, see G. P. Berry, in "Postgraduate Institute on Pneumonia," *Journal of the American Medical Association* 109 (1937): 2063.

25. See Alvin E. Price, "The Modern Treatment of Pneumonia," *Journal of the Michigan State Medical Society* 36 (1937): 77; Russell L. Cecil and Edgar A. Lawrence, "Pneumonia in Private Practice: A Study of 911 Cases," *Journal of the American Medical Association* 111 (1937): 1893; Cyris C. Sturgis, "The Treatment of Pneumonia," *Wisconsin Medical Journal* 37 (1938): 193; MacGregor, "Recent Advances in the Treatment of Pneumonia," 489; John A. Kolmer, "The General and Specific Treatment of Pneumonia," *Texas State Journal of Medicine* 34 (1938): 461; Edward A. Birge, "Serum Therapy of Pneumonia," *Wisconsin Medical Journal* 38 (1939): 287. For the earliest use of such a calculus (indeed, atypical for its own era), see C. C. Pierce, "Hospitalization of Pneumonia Cases: Chicago Ammonia [*sic*] Commission," *Modern Hospital* 25 (1925): 490–92.

26. Birge, "Serum Therapy of Pneumonia," 287. See also William Robert Willard, "An Attempt to Develop a Pneumonia Control Program in New Haven, 1936–1937," Doctor of Public Health thesis, Yale University School of Medicine, 1937, 12 [YU, Y12P11]; Irving, "Reduction of Mortality from Pneumococcus Pneumonia," 11; MacGregor, "Recent Advances in the Treatment of Pneumonia," 488; Levine, "The Opportunity for the Modern Treatment of Lobar Pneumonia in General Practice," 645; Rodney W. Bliss, "Treatment of Pneumonia," *Nebraska State Medical Journal* 24 (1939): 126. For the details of one Pennsylvania practitioner's "pneumonia emergency set," see Luchi, "The General Practitioner and the 1938 Pneumonia Control Campaign," 509–10.

27. MacGregor, "Recent Advances in the Treatment of Pneumonia," 488. See also Julien E. Benjamin, Marion Blankenhorn, James M. Ruegsegger, and Fannie A. Senior, "Study of the Diagnosis and Treatment of Lobar Pneumonia According to Types and Specific Serum Therapy," *Annals of Internal Medicine* 11 (1937): 445; Henry B. Gotten and Richard E. Ching, "The Treatment of Lobar Pneumonia," *Journal of the Tennessee Medical Association* 31 (1938): 354; Ruffin, "The Pneumonia Control Program of the District of Columbia," 383; Cecil, "Present Status of Serum Therapy in Pneumonia," 106–7; Jesse G. M. Bullowa, "Serum Therapy of the Pneumococcic Pneumonias," *Pennsylvania Medical Journal* 42 (1938): 21. Such moral responsibility was even envisioned by one practitioner as soon to emerge into a legal responsibility; see Potts, "Serum Therapy in Lobar Pneumonia," 421.

28. Russell L. Cecil, Jesse G. M. Bullowa, Henry T. Chickering, and E. H. L. Corwin, "Community Provision for the Serum Treatment of Pneumococcic Pneumonias," *Journal*

of the American Medical Association 109 (1937): 1328; Gotten and Ching, "The Treatment of Lobar Pneumonia," 354.

29. For parallel economic roadblocks to the treatment of syphilis with arsenicals at this time, see Allan M. Brandt, *No Magic Bullet: A Social History of Venereal Disease in the United States since 1880, with a New Chapter on AIDS* (New York: Oxford University Press, 1987), 131–32.

30. I. S. Falk, C. Rufus Rorem, and Martha D. Ring, *The Costs of Medical Care: A Summary of Investigations on the Economic Aspects of the Prevention and Care of Illness* (Chicago: University of Chicago Press, 1933), 105.

31. Donald B. Armstrong, Louis I. Dublin, and Elizabeth J. Steele, *The Cost of Medical Care: A Study of Costs in the Families of the Field Employees of the Metropolitan Life Insurance Company* (New York: Metropolitan Life Insurance Company, 1934), 28.

32. Joseph Hirsh, "A Study of the Economics of Pneumonia," *Public Health Reports* 53 (1938): 2157, 2165.

33. Ibid., 2158–60. Russell Cecil and Edgar Lawrence would note that among type I cases on the private wards of seven New York City hospitals from 1928 to 1938, 60 percent received serum, though even this figure was disappointing to them ("Pneumonia in Private Practice," 1891).

34. U.S. Bureau of Census, *Historical Statistics of the United States, Colonial Times to 1957* (Washington, D.C.: U.S. Government Printing Office, 1960), 677. Such events occurred just at the cusp of the rise in such coverage; within a decade, enrollment in hospitalization insurance would rise to include nearly half the population.

35. K. S. Howlett, in Gotten and Ching, " Treatment of Lobar Pneumonia," 356.

36. A. T. McCormack, in J. Shirley Sweeney, "Serum Therapy in Pneumonia," *Texas State Journal of Medicine* 34 (1938): 468; see also Nevil Garrett, in W. J. Shelton, "Lobar Pneumonia," *Kentucky Medical Journal* 36 (1938): 27.

37. Blankenhorn obtained data from the U.S. Public Health Service, the National Drug Company, E. R. Squibb & Sons, Lederle Laboratories, Eli Lilly & Company, and Gilliland Laboratories to calculate that 3.42 billion units of serum had been distributed in 1937. At 100,000 units per case, this amounted to serum to supply 21 percent of the estimated 160,413 cases of type I and II pneumonia for the year (Blankenhorn, "The Present Status of the Serum Therapy of Lobar Pneumonia," 1260). By late 1938, Wheelan Sutliff estimated that "considerably less than 50 percent" of appropriate pneumococcal pneumonia patients in New York City were receiving serotherapy, though serum distribution had "increased approximately 200 percent during the first six months of 1938 over the previous year" (Wheelan D. Sutliff, "Symposium on Serum Therapy in Pneumonia," *The Diplomat* 11 [1939]: 33). Regarding even contemporary difficulties in attempting to quantitate the distribution of serotherapy nationwide, see W. T. Harrison, Chief of Division of Biological Control, "Memorandum for the Director, National Institute of Health," 10/25/37 [RG443 0425, Box 14].

38. "Pneumonia Mortality and Pneumococcus Typing Facilities," *Journal of the American Medical Association* 109 (1937): 1910; see also Kenneth McGill, "Pneumonia Mortality and Health Department Facilities for Typing Pneumococci: Summary with Charts and Tables" [RG443 0425, Box 14].

39. See Roderick Heffron to Louis Dublin, 7/27/37 [LDP, Box 16, "Pneumonia"];

Willard, "An Attempt to Develop a Pneumonia Control Program in New Haven, 1936–1937," 32–33 [YU, Y12P11].

40. See, e.g., the Commonwealth Fund's assessment of the situation in Michigan, in Barbara S. Quin, "Memorandum," 6/17/35 [Box 202, Folder 1900, Series 18.1 (Grants), RAC]; Thomas Parran, "Pneumonia Conference: Opening Statement," 11/12/37 [RG443 0425, Box 14].

41. See Louis I. Dublin and Alfred J. Lotka, *The Money Value of a Man* (New York: Ronald Press Company, 1930); I. S. Falk, *Security Against Sickness: A Study of Health Insurance* (Garden City, N.Y.: Doubleday, Duran, and Company, 1936), 3–35; Andrew S. Wong, "A Statistical Survey of Pneumonia in the Territory of Hawaii," Master of Public Health thesis, Yale University School of Medicine, 1938, 62–63 [YU, Y12PM12]. Of course, the general notion of the societal economic benefits to accrue from investment in public health had been circulating for far longer. See, e.g., George Rosen's analysis of the Benthamites Edwin Chadwick and Southwood Smith in *A History of Public Health,* expanded ed. (Baltimore: Johns Hopkins University Press, 1993), 182–89. Regarding the resurgence of such an ethos in the first decades of the twentieth century in America, see E. Richard Brown, *Rockefeller Medicine Men: Medicine and Capitalism in America* (Berkeley: University of California Press, 1979), 112–19; Elizabeth Fee, "The Origins and Development of Public Health in the United States," in *Oxford Textbook of Public Health,* 3rd ed., *Volume I: The Scope of Public Health* (New York: Oxford University Press, 1997), 39. Regarding the fear of retrenchment of such public health investment (and of the "false economy" of such retrenchment) in the wake of the Depression, see Louis I. Dublin, "The Health of the People in a Year of Depression," *American Journal of Public Health* 22 (1932): 1128–32; idem, "The Cost of Public Health Service—Can We Afford to Reduce It? [Radio Talk, Station KPO, San Francisco]," 9/9/34 [LDP, Box 4, "American Public Health Association"].

42. Alvin E. Price, "The Serum Treatment of Lobar Pneumonia," *Journal of the Michigan State Medical Society* 34 (1935): 761–62. In Price's study of serum usage in Detroit in 1935, hospitalization stays were apparently reduced from 14.9 to 12.6 days through the usage of serum, at a savings of $9.66 per case (partially offsetting the $43.88 average serum cost per patient). Price would conclude in a more absolutist tone: "The reduction in mortality and the lives saved more than compensate for the additional cost of serum."

43. Jesse G. M. Bullowa, in "Postgraduate Institute on Pneumonia," 1937, 2062. See also Ruffin, "The Pneumonia Control Program of the District of Columbia," 383; Charles L. Eshelman, "Recent Advances in the Treatment of Pneumonia," *New Orleans Medical and Surgical Journal* 91 (1938): 80; Kolmer, "The General and Specific Treatment of Pneumonia," 464; A. S. Brady, in MacGregor, "Recent Advances in the Treatment of Pneumonia," 492; Millard Knowlton, "The Problem of Serum for Pneumonia," *Connecticut Health Bulletin* 52 (1938): 10; and H. C. Hinshaw, "Recent Advances in the Treatment of Pneumonia," *Proceedings of the Staff Meetings of the Mayo Clinic* 13 (1938): 370. Administered with only a slightly less moral tone than such proclamations would be the continued invocation of the analogy to appendicitis: not only should pneumonia be considered an emergency like appendicitis, but both physicians and the lay public alike should deem the expenses of antipneumococcal serotherapy as necessary as the cost of surgery. See V. E. Mace, "The Treatment of Pneumococcic Pneumonia," *West Virginia Medical Journal* 32 (1936): 260–61;

Sutliff, "Type-Specific Anti-Pneumococcic Serum Therapy," 513; Rufus Cole, "Possibilities for Pneumonia Control as Indicated by Present Scientific Knowledge," *Military Surgeon* 81 (1937): 247; Jesse G. M. Bullowa and Murray J. Hanigsberg, "Serum Therapy for Pneumococcus Type I Pneumonia," *New York State Journal of Medicine* 37 (1937): 724; Levine, "The Opportunity for the Modern Treatment of Lobar Pneumonia in General Practice," 647; "The Treatment of Pneumonia," *New Orleans Medical and Surgical Journal* 91 (1938): 250; Gotten and Ching, "The Treatment of Lobar Pneumonia," 354.

44. Bullowa, "Pneumonias: Their Management," 368. Cole would upgrade the value of such lives saved annually to $30 million ("Possibilities for Pneumonia Control as Indicated by Present Scientific Knowledge," 247). Charles Camac, Bellevue's medical director, had rendered the first such analysis as applied to antipneumococcal antiserum in 1923 (C. N. B. Camac, "Antipneumococcus Serum in Lobar Pneumonia. A Clinical Report," *American Journal of Medical Science* 166 [1923]: 541). For a discussion of parallel contemporary justifications for investing in the treatment of syphilis, see Brandt, *No Magic Bullet,* 133–35. Again, for a parallel contemporary analysis supporting increased public health expenditures in general, see Dublin and Lotka, *The Money Value of a Man,* 123–37.

45. Knowlton, "The Problem of Serum for Pneumonia," 7. Knowlton had long been an enthusiastic supporter of both antipneumococcal serotherapy and the transformation of pneumonia into a public health concern. See Millard Knowlton to Simon Flexner, 1/19/26 [RCP, filed under "Knowlton, Millard"]; Roderick Heffron to Millard Knowlton, 1/22/35; Millard Knowlton to Roderick Heffron, 1/23/35 [both in TPP, Box 16, FF 147].

46. Knowlton, "The Problem of Serum for Pneumonia," 10. Knowlton would also protest the relative ease with which the state funded the treatment of tuberculosis versus pneumonia.

47. Ibid., 10. Lending the requisite moral weight to his argument, Knowlton would add: "Even the cost of funerals might exceed the cost of serum" (ibid., 11).

48. Kolmer, "The General and Specific Treatment of Pneumonia," 464. Such rhetoric, of course, differed little from that voiced by Henry Nichols over two decades earlier (as discussed in chapter 1). See Henry J. Nichols, "The Lobar Pneumonia Problem in the Army from the Viewpoint of the Recent Differentiation of Types of Pneumococci," *Military Surgeon* 41 (1917): 155.

49. With the steady decline in tuberculosis mortality, pneumonia (reported as combined "lobar" and "bronchopneumonia," despite the influence of Cole) had nationally surpassed tuberculosis for good in 1928. See Forrest E. Linder and Robert D. Grove, *Vital Statistics Rates in the United States, 1900–1940* (Washington, D.C.: U.S. Government Printing Office, 1943), 210–42.

50. Hirsh, "A Study of the Economics of Pneumonia," 2153.

51. Edward S. Rogers, in Julien E. Benjamin, Marion Blankenhorn, and Fanny A. Senior, "The Results of the Treatment of Pneumonia with Specific Therapeutic Serum," *Ohio State Medical Journal* 33 (1937): 41. See also Edward S. Rogers, "The New York State Program for the Control of Pneumococcus Pneumonia," *American Journal of Public Health* 27 (1937): 136.

52. Regarding "greatest advance," see Plummer, "The Use of Serum in the Treatment of the Higher Types of Pneumonia," 696; regarding "great gap," see Cecil, "Effects of Very

Early Serum Treatment in Pneumococcus Type I Pneumonia," 692. See also A. J. Lanza, "Newer Methods of Diagnosis and Treatment of Pneumonia," *Journal-Lancet* 56 (1936): 519.

53. Cole, "Possibilities for Pneumonia Control as Indicated by Present Scientific Knowledge," 249.

54. Daniel S. Hirshfield, *The Lost Reform: The Campaign for Compulsory Health Insurance in the United States from 1932 to 1943* (Cambridge, Mass.: Harvard University Press, 1970), 42–70.

55. Ibid., 100–103.

56. Ibid., 104–34. See also Interdepartmental Committee to Coordinate Health and Welfare Activities, *Proceedings of the National Health Conference, July 18, 19, 20, 1938* (Washington, D.C.: U.S. Government Printing Office, 1938).

57. Their movement in this direction would ultimately be shaped most forcefully by the introduction of the Wagner Bill in 1939. See "Platform of the AMA," *Journal of the American Medical Association* 113 (1939): 2060; Hirshfield, *The Lost Reform,* 146–49; James G. Burrow, *A.M.A.: Voice of American Medicine* (Baltimore: Johns Hopkins University Press, 1963), 215–27.

58. Hirshfield, *The Lost Reform,* 127–30. For the misreading by overly optimistic Parran confidante Paul DeKruif of Roosevelt's concerns regarding health care (and DeKruif's consequent increasing bitterness toward the nation's "Skipper"), see Paul De Kruif to Thomas Parran, 12/5/37; Paul De Kruif to Thomas Parran, 11/17/38 (with attached "Memorandum to the President"); Paul De Kruif to Thomas and Carroll Parran, 11/26/38; Paul De Kruif to Thomas and Carroll Parran, 12/10/38 [all in TPP, Box 1, FF 4].

59. Edwin E. Witte, *The Development of the Social Security Act* (Madison: University of Wisconsin Press, 1962), 173.

60. See Hirshfield, *The Lost Reform,* 152. Regarding the increased funding proposed and passed under bill H.R. 6635, see *Congressional Record: Proceedings and Debate of the 76th Congress, 1st Session* 84 (1939), 8830. Regarding the ill-fated history of the more comprehensive Wagner Bill at this time, as well as Parran's own opposition to it, see Hirshfield, *The Lost Reform,* 135–65; Jonathan Engel, *Doctors and Reformers: Discussion and Debate over Health Policy, 1925–1950* (Columbia: University of South Carolina Press, 2002), 140–86.

61. See Brandt, *No Magic Bullet,* 143, 155; See also Roy Lubove, "The New Deal and National Health," *Current History* 45 (1963): 83; Fitzhugh Mullan, *Plagues and Politics: The Story of the United States Public Health Service* (New York: Basic Books, 1989), 102–7; Elizabeth Fee, "Designing Schools of Public Health for the United States," in *A History of Education in Public Health: Health that Mocks the Doctors' Rules,* ed. Elizabeth Fee and Roy M. Acheson (New York: Oxford University Press, 1991), 184–85; Elizabeth Fee and Barbara Rosenkrantz, "Professional Education for Public Health in the United States," in ibid, 230–32; John Duffy, *The Sanitarians: A History of American Public Health,* 257–260; Elizabeth Fee, "The Origins and Development of Public Health in the United States," 43–44.

62. Thomas Parran, "Expanding Frontiers of Health [Broadcast, New York Medical Society, WABC, New York City, 4/29/36]," [TPP, Box 35, FF 408].

63. Thomas Parran, "Address [delivered before the Missouri Public Health Association, 5/14/38]," [TPP, Box 38, FF 487]. Initially, Parran had written that the "average person," rather than the "individual," would be unable to pay for the serum. Generalizing, he con-

tinued: "The growth of medical science has had several results; first, it has increased the cost thereby putting off an increasing number of people; second, it has increased the necessity for providing something alike in serum, x-ray material, or tests at a laboratory and has necessitated the proof of these expensive items of equipment and facilitates [*sic*]; third, it has necessitated also the collaboration of many specialists and this change in health and medical relationships naturally has brought some pains and difficulties in such relationships, all of which have not been worked out."

64. Thomas Parran, "Medicine in a Changing World [Address before Sesquicentennial, Georgetown University, 6/1/39]," [TPP, Box 40, FF 521]. Nearly the same phraseology had been used by Parran before the Massachusetts Medical Society in 1938; see Thomas Parran, "The Work and Aims of the United States Public Health Service," *New England Journal of Medicine* 219 (1938), 75. See also Thomas Parran, "The Significance of the National Health Conference [delivered at the National Health Conference, 7/18/38]," [TPP, Box 39, FF 492]; Thomas Parran, "The Road Ahead in Public Health [delivered at Detroit Town Hall, 12/7/38]," [TPP, Box 39, FF 501]. For the broader emergence of this concept among Western nations at the time, see Oswei Temkin, "Health and Disease," in *The Double Face of Janus and Other Essays in the History of Medicine* (Baltimore: Johns Hopkins University Press, 1977), 437–38.

65. Thomas Parran, "Medicine in a Changing World," [TPP, Box 40, FF 521]. Earlier, he had declared that "we are witnessing now a renaissance in public health" ("Commencement Address, Skidmore College, 6/6/38," [TPP, Box 39, FF 491]). Before the American Public Health Association in October of 1938, he declared: "Public health has become a people's cause. The people have become insistent that they be given the benefits of what scientific knowledge has verified as valuable for the prevention and relief of disease and for the maintenance of healthful living" ("The Health of the Nation," *American Journal of Public Health* 28 [1938]: 1380). In a candid letter to Paul De Kruif six weeks later, however, Parran continued to contrast the public and political responses to epidemic versus endemic diseases in noting the actual difficulty of proving to the American people the need for such public health expansion:

> Supporting most proposals for governmental action are important pressure groups —the aged for pensions, the farmers for soil conservation, and even the armament manufacturers for national defense. It is true that for a health program, we should have the whole country as a pressure group. Unfortunately, however, people do not yet realize the specific impact of public health measures on them as individuals. It is always the other fellow who is apt to be sick, to get tuberculosis or to contract pneumonia. Most of the early health activities were initiated in response to the fear motive, an epidemic of cholera or typhoid fever, etc. The medical care part of the program will appeal to the under-privileged but we have not yet shown the great middle class how they will benefit. (Thomas Parran to Paul De Kruif, 12/2/38 [TPP, Box 1, FF 4]).

66. J. Shirley Sweeney, "Serum Therapy in Pneumonia," 464. Few practitioners, however, shared as much faith in the need for an expanded public health system as the head of Illinois' Pneumonia Control Program, who asserted, a year later: "Public health is pro-

gressing and broadening its scope to include many diseases outside of those that are definitely contagious. Each year more medical problems are recognized as belonging in the field of public health, and only by attacking them in this way is it possible to make headway in reducing the mortality and morbidity of the forces which make up the 'Battalion of Death'" (Howard A. Lindberg, "The Illinois Pneumonia Control Program," *Illinois Medical Journal* 76 [1939]: 85).

67. Morris Fishbein, in *Proceedings of the National Health Conference,* 117–18.

68. Thomas Parran, "Public Health Today [Address Given before the International Medical Assembly of the Inter-State Post-Graduate Medical Association, St. Paul, 10/14/36]," [TPP, Box 35, FF 412].

69. Ibid.

70. "Statement of Thomas Parran, Surgeon General, United States Public Health Service," in *Investigation and Control of Pneumonia, Influenza, and the Common Cold: Hearings before a Subcommittee of the Committee on Education and Labor, United States Senate* (Washington, D.C.: U.S. Government Printing Office, 1940), 30; "Statement of Dr. H. A. Holle, National Institute of Health," ibid., 9. See also "Statement of Dr. Felix J. Underwood, Executive Officer and Secretary, Mississippi State Board of Health, Jackson, Miss.," ibid., 41; "Statement of Dr. H. A. Lindberg, Director, Division of Pneumonia Control, Illinois State Department of Health," ibid., 51–52. It does not appear that the proposed bill, S.3914, made it out of the Senate Committee on Education and Labor. See *Congressional Record: Proceedings and Debates of the 76th Congress, 3rd Session* 86 (1940): 5424.

71. See, e.g., Lucy S. Heathman, O. McDaniel, and A. J. Chesley, "Pneumonia in Minnesota: What Can be Done About It?" *Minnesota Medicine* 20 (1937): 2–3; *66th Annual Report of the Commissioner of the Michigan Department of Health for the Fiscal Year Ending June 30, 1938* (Lansing, Mich.: Franklin Dekleine Company, 1940), 75; Wong, "A Statistical Survey of Pneumonia in the Territory of Hawaii," 66 [YU, Y12PM12]; Roy L. Cleere, in Claude D. Head, "Serum Therapy in Pneumococcic Pneumonia and Reduction in Pneumonia Mortality," *Rocky Mountain Medical Journal* 36 (1939): 22–23; *22nd Annual Report of the [Illinois] Department of Public Health, July 1, 1938–June 30, 1939,* 70; *Annual Report of State Department of Health, Commonwealth of Virginia for the Year Ending June 30, 1940* (Richmond: Division of Purchase and Printing), 27–28; Harrison F. Flippin, "Modern Control of Pneumonia," *Journal of the Missouri Medical Association* 38 (1941): 399.

72. Brandt, *No Magic Bullet,* 143–44; Georgiana Feldberg, *Disease and Class: Tuberculosis and the Shaping of Modern North American Society* (New Brunswick, N.J.: Rutgers University Press, 1995), 176–81.

73. See the admittedly biased "Progress of Programs for Pneumonia Control," *Bulletin of Lederle Laboratories* 6 (1938): 118; see also Wong, "A Statistical Survey of Pneumonia in the Territory of Hawaii," 3 [YU, Y12PM12]. From 1937 through 1939, one Yale University School of Public Health thesis each year was devoted to pneumonia control. See, in addition to William Robert Willard's and Andrew S. Wong's previously cited theses, James Clement Hart, "The Program for Control of Pneumonia in New Haven," Master of Public Health thesis, Yale University School of Medicine, 1939, [YU, Y12PM15].

74. Donald B. Armstrong to Thomas Parran, 12/12/36 [RG443 0425, Box 14]. Strong linkages remained between the federal government and Met Life's Influenza and Pneu-

monia Commission; for instance, George McCoy, the director of the NIH, would continue to serve on the commission. See Lewis Ryers Thompson to Donald B. Armstrong, 4/19/37; Donald B. Armstrong to Lewis Ryers Thompson, 4/21/37 [both RG443 0425, Box 14].

75. Thomas Parran to Donald B. Armstrong, 3/25/37 [RG443 0425, Box 14]. Armstrong preferred not to use the term "campaign," more humbly hoping to deliver "advice and guidance" for those hoping to emulate the Massachusetts and New York efforts (Donald B. Armstrong to Thomas Parran, 3/26/37 [RG443 0425, Box 14]). Parran, who seemed to have few reservations about leading such a "campaign," nevertheless attempted to portray it as deriving from the interests of the "state and local health authorities [who] expressed a desire to undertake such parts of pneumonia control programs as may be feasible." See Thomas Parran to Commonwealth Fund, 4/17/37 [RG90 042532, Box 528].

76. *Pneumonia: Mortality and Measures for Prevention* (Washington, D.C.: Government Printing Office, 1938), 31. See also "Parran Urges Funds for War on Pneumonia," *Washington Post,* 13 November 1937, 17. Regarding the AMA, Armstrong cited to Parran the hesitation of Secretary Olin West in particular, based on West's discussion with physicians disinclined to use serotherapy based upon its cost and excessive specificity (Donald B. Armstrong to Thomas Parran, 3/5/37 [RG443 0425, Box 14]).

77. *Proceedings of the National Health Conference, July 18, 19, 20, 1938,* 33–34.

78. Ibid., 36–37. $43 million was recommended for tuberculosis, $47 million for venereal disease, $25 million for cancer, $10 million for malaria, $10 million for mental hygiene, and $20 million for industrial hygiene.

79. Largely through Title VI funds, federal support of the state pneumonia control programs grew from $11,771 in 1937 to $118,696 in 1938; $424,326 in 1939; and $659,057 in 1940. See *Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1937* (Washington, D.C.: U.S. Government Printing Office, 1937), 17; *Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1938* (Washington, D.C.: U.S. Government Printing Office, 1938), 19; *Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1939* (Washington, D.C.: U.S. Government Printing Office, 1939), 24; *Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1940* (Washington, D.C.: U.S. Government Printing Office, 1940), 17.

80. Ibid. As an example of Parran's own nudging of state health officers regarding their efforts towards pneumonia control, see Parran to J. N. Baker (Alabama Department of Health), 4/23/40 [RG443 0425, Box 14].

81. In contrast, other state departments of health would throughout the era continue to bemoan the lack of funding for pneumonia control; it is unclear why they, in particular, were unable to avail themselves of federal funding. See, e.g., Department of Public Health, State of Wyoming, *Biennial Report, 1939–1940,* 62–3.

82. *22nd Annual Report of the [Illinois] Department of Public Health, July 1, 1938–June 30, 1939,* 7; see also Lindberg, "The Illinois Pneumonia Control Program," 85.

83. *17th Annual Report of the [Illinois] Department of Public Health, July 1, 1933–June 30, 1934,* 39; *22nd Annual Report,* 69. It is unclear to what degree the relative emphasis on polyvalent serum use in Illinois may have likewise contributed to the previous lack of typing.

A parallel transformation, in the setting of the private influx of funding through the Commonwealth Fund, could be found in Michigan at the same time. Cf. Barbara S. Quin, "Memorandum," 6/17/35; C. C. Young to Graham Taylor, 2/16/37 [both in Box 202, Folder 1900, Series 18.1 (Grants), RAC]; *67th Annual Report of the Commissioner of the Michigan Department of Health for the Fiscal Year Ending June 30, 1939* (Lansing: Franklin Dekleine Company, 1940), 402–03.

84. Harry Dowling, "The Rise and Fall of Pneumonia-Control Programs," *Journal of Infectious Diseases* 127 (1973): 203; Rufus Cole to Wheelan Sutliff, 12/9/37; Rufus Cole to Roderick Heffron, dated by Cole as 1/30/37, though more likely sent 1/30/38 [both in RCP].

85. "The way things seem to be shaping up now, so far as the country as a whole is concerned, would indicate that in the next few years there is going to be a great deal more work done all over the country than ever previously. . . . Through the Public Health Service direct evidence has been obtained that in almost half the states in the country pneumonia programs are either under way or some serious effort is being made to develop work of this nature along some line or another. In some of the states the work is pretty slim to be sure, but a beginning is better than nothing" (Roderick Heffron to Maxwell Finland, 12/22/37 [Series II, Subseries A, Box 2, Folder 41, MFP]).

86. Dowling, "The Rise and Fall of Pneumonia-Control Programs," 204.

87. Willard, "An Attempt to Develop a Pneumonia Control Program in New Haven, 1936–1937," 30 [YU, Y12P11]; Henry D. Chadwick, "Lay Publicity Concerning Serum Treatment of Pneumonia," *New England Journal of Medicine* 218 (1938): 136; Lindberg, "The Illinois Pneumonia Control Program," 88. Cf. with Rogers, in Benjamin et al., "The Results of the Treatment of Pneumonia with Specific Therapeutic Serum," 41; Benjamin et al., "Study of the Diagnosis and Treatment of Lobar Pneumonia According to Types and Specific Serum Therapy," 438, 446.

88. Flippin, "Modern Control of Pneumonia," 399. Further motivation for preaching directly and accurately to the laity stemmed from concerns regarding "articles . . . beginning to appear in national periodicals" ("Pneumonia Publicity," *New England Journal of Medicine* 218 [1938]: 132).

89. See, for example, *New Methods for Pneumonia Control: Reproduction of Charts Shown in the Scientific Exhibit at the Annual Meeting of the American Medical Association, San Francisco, June 13–17, 1938* (New York: Metropolitan Life Insurance Company, 1938); *Pneumonia: Some Important Facts Regarding Treatment and Control* (Washington, D.C.: U.S. Government Printing Office, 1940). Such commercial serum providers as Lederle likewise lent their marketing expertise: "They tell us that over 7,000,000 people went through the health exhibits at the World's Fair, and our Pneumonia Exhibit was universally well regarded" (R. S. Childs, Lederle Laboratories, to Rufus Cole, 3/5/40 [RCP, filed under "Lederle Laboratories"]).

90. *A New Day in Health Protection,* 2–5; *Press Book: A New Day,* 4–9 [both in MLIC, Box 160605]; Donald B. Armstrong to "Health and Social Agencies," 2/11/41 [RG112, Entry 29, Box 241, Folder 710].

91. Edward L. Bortz, "Pneumonia in Pennsylvania," *Transactions of the American Clinical and Climatological Association* 56 (1940): 110. In Massachusetts, by 1940, it was con-

sidered that further "promotional work" was becoming less relevant in the context of increasingly informed physician and lay populaces (Commonwealth of Massachusetts, *26th Annual Report of the Department of Public Health of Massachusetts,* 82).

92. Georgia, Idaho, and Kansas, for example, provided only typing services. See State of Georgia Department of Public Health, *Annual Report, 1938,* 64; Idaho Department of Public Welfare, Division of Public Health, *Biennial Report, 1937–1938,* 15; *Biennial Report of the Department of Public Welfare of the State of Idaho, 1939–1940,* 22; State Board of Health of the State of Kansas, *Twentieth Biennial Report, July 1, 1938, to June 30, 1940,* 140; Kansas State Board of Health, *Twenty-First Biennial Report, July 1, 1940, to June 30, 1942,* 75 (note the frequent name changes of such public health reports throughout the era). At the other end of the spectrum of "control," in Massachusetts, by 1937, physicians who reported pneumonia deaths but who had not requested serum from the state were directly contacted by the public health department to discuss the issue (Commonwealth of Massachusetts, *23rd Annual Report of the Department of Public Health for the Year Ended November 30, 1937,* 8). A sample circular read: "Recently you had under your care cases of lobar pneumonia that resulted fatally. The Department is neither aware of nor concerned with the details of these cases. We are, however, interested in reaching directly those physicians who are treating cases of pneumonia, as experience shows that many of these physicians are not aware of the advantages of serum treatment in certain cases," in Henry D. Chadwick to Lucy F. Forrer, 5/24/37 [Box 184, Folder 1736, Series 18.1 (Grants), RAC].

93. Such states, in Charles V. Chapin's 1915 "ranking" of state public health work, had ranked 1st through 5th, respectively (Chapin, *A Report on State Public Health Work Based on a Survey of State Boards of Health* [Chicago: American Medical Association], 196–97).

94. In Chapin's study, North Dakota and Iowa had ranked 34th and 29th, respectively; whereas Indiana and California had ranked 6th and 20th. See also North Dakota State Department of Health, *Twenty-Fifth Biennial Report, July 1, 1936 to June 30, 1938,* 38; North Dakota State Department of Health, *Twenty-Seventh Biennial Report, July 1, 1940 to June 30, 1942,* 16–19; State of Iowa, *Report of the State Department of Health for the Biennial Period Ending June 30, 1938,* 28–33; State of Iowa, *Report of the State Department of Health for the Biennial Period Ending June 30, 1940,* 28–32.

95. Commonwealth of Massachusetts, *26th Annual Report of the Department of Public Health of Massachusetts,* 51; Commonwealth of Massachusetts Department of Public Health, "Pneumonia Program for 1940"; Commonwealth of Massachusetts Department of Public Health, "Pneumonia Program for 1941" [latter two located in the Countway Medical Library, Call Number 11.Z.1940.1]

96. State of New York, *60th Annual Report of the Department of Public Health for the Year Ending December 31, 1939,* I:13–14.

97. Tennessee Department of Public Health and the Tennessee State Medical Association, *Pneumonia: Its Etiology, Diagnosis, and Treatment* (1940), 15–16, 30–31 [located in the National Library of Medicine, Call Number WC 202 T297p 1940]; *Biennial Report of the Department of Public Health, State of Tennessee, for the Fiscal Years 1939–1941,* 62–63. Of interest, on the basis of a request in 1938 by Tennessee State Commissioner of Health W. C. Williams for assistance with tuberculosis control and for the provision of funds for antipneumococcal antiserum, the Commonwealth Fund had by 1939 financed a "special" pneu-

monia control program in Sumner County, Tennessee, with antipneumococcal antiserum made available to local physicians. But by 1939, when the Fund initially refrained from providing the potentially toxic sulfa drugs, Williams had to plead repeatedly to them on sulfapyridine's behalf (the Fund finally acceded by the latter half of 1939). By 1940, when the state program was formulated and despite the declaration that the "experience gained in Sumner County was of much value in planning the state-wide Pneumonia Control Program," it would be antiserum that was not provided at the state level. See W. C. Williams to Clarence Scamman, 10/1/38; W. C. Williams to Clarence Scamman, 6/27/39; W. C. Williams to Clarence Scamman, 8/25/39; Clarence Scamman to W. C. Williams, 10/26/39 [all in Box 36, Folder 520, Series 12.2, RAC]; *Biennial Report of the Department of Public Health, State of Tennessee, for the Fiscal Years 1939–1941,* 63–64.

98. *Biennial Report of the Department of Public Health, State of Tennessee, for the Fiscal Years 1943–1945,* 58. Of the continuing Sumner County program, it would be noted: "In the second year of the program, the physicians appeared to have become familiar with the use of the sulfonamides, the drugs were easily available, and fewer consultation services were asked of the Health Department in cases of pneumonia" (R. H. Hutcheson to Clarence Scamman, 3/25/44 [Box 36, Folder 522, Series 12.2, RAC]).

PART III. RESOLUTION

1. See, as early as 1947, Richard Shryock's *The Development of Modern Medicine: An Interpretation of the Social and Scientific Factors Involved* (New York: Alfred A. Knopf, 1947), 448–49; see also Shryock, *American Medical Research Past and Present* (New York: Commonwealth Fund, 1947), 206; Perrin Long, Introduction to Iago Galdston, *Behind the Sulfa Drugs: A Short History of Chemotherapy* (New York: D. Appleton-Century, 1943), viii. Cf. ibid., 141.

2. W. D. Foster, *A History of Medical Bacteriology and Immunology* (London: Heinemann Medical, 1970), 171. Instead, Foster ascribed antipneumococcal serotherapy's utility to the impetus it gave to fundamental research on the pneumococcus (165–71). For an early, complete, and telling ignoring of antipneumococcal serotherapy, see Harry E. Ungerleider, Henry W. Steinhaus, and Richard S. Gubner, "Public Health and Economic Aspects of Pneumonia: A Comparison with Pre-Sulfonamide Years," *American Journal of Public Health* 33 (1943): 1093–1102. Fifty years later, Leonard D. Epifano and Robert D. Brandstetter would write: "Therapeutic application of the typing of the pneumococcus by the development of antisera was delayed until 1944, which proved to be ill-timed because the clinical use of already discovered bacterial agents was under way." See "Historical Aspects of Pneumonia," in *The Pneumonias,* ed. Monroe Karetzky, Burke A. Cunha, and Robert D. Brandstetter (New York: Springer-Verlag, 1993), 11; see also, M. Weatherall, *In Search of a Cure: A History of Pharmaceutical Discovery* (New York: Oxford University Press, 1990), 141–42. The kindest assessment—beyond those by Harry Dowling—appears in Lewis Thomas's autobiography, in which he reflects on the efforts of his fellow interns and himself in combating the pneumococcus with antiserum at Boston City Hospital in 1937: "The commonest [treatable illness], and the illness requiring the hardest and most urgent work by the intern, was lobar pneumonia. . . . It didn't always come out [successfully], but it was

successful enough to make it worth great effort. An intern was judged by his superiors on this kind of success more than by any other quality: if your lobar pneumonia cases were well handled, you were likely to have a future; if not, not" (Lewis Thomas, *The Youngest Science: Notes of a Medicine-Watcher* [New York: Viking Press, 1983], 41–44).

3. Even Dowling and Thomas would render such characterizations of the near-immediate transition from serotherapy to chemotherapy. See Harry F. Dowling, "The Rise and Fall of Pneumonia-Control Programs," *Journal of Infectious Diseases* 127 (1973): 203; Thomas, *The Youngest Science,* 35.

4. William Bell, cited in Tom Mahoney, *The Merchants of Life: An Account of the American Pharmaceutical Industry* (New York: Harper and Brothers, 1959), 169, 170.

5. Mahoney's text itself was published the very year that many of the nation's leading pharmaceutical executives began to find themselves defending their practices (especially pricing) before Senator Estes Kefauver and the Senate Subcommittee on Antitrust and Monopoly. See, as an introduction, Richard Harris, *The Real Voice* (New York: Macmillan, 1964). Three years later, amidst the same ongoing Kefauver hearings, Wilbur Malcolm, president of American Cyanamid (which included Lederle Laboratories, whose serum efforts Malcolm himself had headed three decades previously), used antipneumococcal antiserum, along with the sulfa drugs and penicillin themselves, to demonstrate the "rapid obsolescence of drugs" that warranted elevated drug prices. In his testimony, however, Malcolm reported that $800,000 in serum sales was achieved in 1939 (the year sulfapyridine was introduced to the American market). After a dip to as low as approximately $300,000 worth of annual sales by 1942, sales increased (due to government wartime purchases) to as high as $600,000 for 1944 before dropping off entirely by the end of the war. See "Statement of W. G. Malcolm," United States Congress, Senate Committee on the Judiciary, Subcommittee on Antitrust and Monopoly, *Administered Prices, Part 24: Administered Prices in the Drug Industry (Antibiotics),* 86th Congress, 2nd session, 1960, 13633–37.

Chapter 6. Histology of a Revolution

1. Angelo L. Luchi, "The General Practitioner and the 1938 Pneumonia Control Campaign" (Presentation before the Pennsylvania State Medical Society, October 5, 1938), *Pennsylvania Medical Journal* 42 (1939): 512. Note that given the concentrated timing of events entailed, for the citations in this chapter, the dates of oral presentations will be included along with the actual publication dates of the papers based on them.

2. M. Herbert Barker, "The Role of Serum and Oxygen in Pneumonia" (Presentation before the Indiana State Medical Association, October 5, 1938), *Journal of the Indiana State Medical Association* 32 (1939): 1–2. Similarly, an Oklahoma City practitioner, reporting in late 1938 before the Southern Medical Association of the choice between serotherapy and the first of the sulfa drugs, sulfanilamide, for the treatment of pneumonia, would clearly advocate for antiserum as having endured several decades of testing in contrast to the uncertain merits of the sulfa drugs. In Lewis J. Moorman, "Pneumonia: Medical Treatment" (Read before the Southern Medical Association, November 15–18, 1938), *Southern Medical Journal* 32 (1939): 1216–17.

3. See William. H. Kelley and J. W. Regan, "Sulfapyridine in the Treatment of Lobar

Pneumonia" (Presentation before the Tri-State Medical Association of the Carolinas and Virginia, February 20–21, 1939), *Journal of Southern Medicine and Surgery* 101 (1939): 357; Perrin H. Long and W. Barry Wood Jr., "Observations upon the Experimental and Clinical Use of Sulfapyridine. II. The Treatment of Pneumococcal Pneumonia with Sulfapyridine," *Annals of Internal Medicine* 13 (1939): 493–94. See also "Proposed Pneumonia Work for 1938–1939," 11/22/38 [Box 203, Folder 1902, Series 18.1 (Grants), RAC]. The correspondence between the members of Michigan's state pneumonia program and the Commonwealth Fund, which began funding the program's activities in 1937 and would continue to do so throughout the sulfonamide "revolution," is particularly enlightening regarding evolving opinions regarding serotherapy and chemotherapy throughout the era.

4. Robert Hoffman, "Serum Therapy of Pneumonia" (Presentation before the Section on Medicine of the Indiana State Medical Association, October 11, 1939), *Journal of the Indiana State Medical Association* 32 (1939): 687.

5. Harry Dowling, *Fighting Infection: Conquests of the Twentieth Century* (Cambridge: Harvard University Press, 1977), 105–10.

6. James Harvey Young, "Sulfanilamide and Diethylene Gycol," in *Chemistry and Modern Society,* ed. John Parascandola and James C. Whorton (Washington, D.C.: American Chemical Society, 1983), 106–7; Barron H. Lerner, "Scientific Evidence versus Therapeutic Demand: The Introduction of the Sulfonamides Revisited," *Annals of Internal Medicine* 115 (1991): 317.

7. For therapy against all serotypes, see D. J. Louis, "The Treatment of Pneumonias with Sulfanilamide," *Illinois Medical Journal* 73 (1938): 422–25; Alvin E. Price and Gordon B. Myers, "Treatment of Pneumococcic Pneumonia with Sulfanilamide," *Journal of the American Medical Association* 112 (1939): 1021–27. For therapy against type III pneumococci, see J. H. L. Heintzelman, Philip B. Hadley, and Ralph R. Mellon, "The Use of P-Aminobenzenesulphonamide in Type 3 Pneumococcus Pneumonia," *American Journal of Medical Science* 193 (1937): 759–63; Joseph F. Sadusk, "Observations on Sulfanilamide Therapy in Pneumonia and Meningitis due to Type 3 Pneumococcus," *New England Journal of Medicine* 219 (1938): 787–90; Maxwell Finland and John W. Brown, "Treatment of Pneumococcus Type 3 Pneumonia with Specific Serum and Sulfanilamide," *New England Journal of Medicine* 220 (1939): 369–72. Regarding U.S. Public Health Service interest in conducting alternate control trials of the use of the combination of serotherapy and sulfanilamide versus serum alone for pneumococcal pneumonia, see Carl Voegtlin to Doctor Thompson, 5/25/37; Sanford R. Rosenthal to Carl Voegtlin, received 6/2/37 [both in RG443 0425, Box 14].

8. For its frequent use in New Haven between 1937 and 1939, e.g., see James Clement Hart, "The Program for Control of Pneumonia in New Haven," Master of Public Health thesis, Yale University School of Medicine, 1939, 23, 72 [YU, Y12PM15].

9. Maxwell Finland to Wesley Spink, 10/28/37 [Series II, Subseries A, Box 5, Folder 8, MFP].

10. Wesley Spink to Maxwell Finland, 12/13/37 [Series II, Subseries A, Box 5, Folder 8, MFP].

11. Bullowa was commenting on the rough draft of an article by Dublin (for *Colliers* magazine) concerning the clinical approach to pneumonia (Jesse Bullowa to Louis Dublin,

undated but likely summer, 1937 [LDP, Box 16, "Pneumonia"]). Wrote Lloyd Felton to Dublin of the same draft: "Even in the case of Type III insufficient number have been treated to show definitely that it is of value. Certainly in our experimental work with this compound, even with this type of pneumococcus, the action is minimal. I have tested a great many organic chemicals which have as much activity against Type III as sulfanilamide, and yet I never have thought it worth while to make a clinical trial. . . . I say this with considerable feeling, because you well realize that it took ten years to show definitely that the best form of pneumonia serum that we have today, that is, the concentrate, materially decreases [the] mortality rate" (Lloyd D. Felton to Louis Dublin, 7/20/37 [LDP, Box 16, "Pneumonia"]).

12. Alvin E. Price, "Pneumonia. Use of Antipneumococcus Serum," 11/14/38, accompanying J. T. Tripp to Elliott S. Robinson, 11/23/38 [Box 203, Folder 1902, Series 18.1 (Grants), RAC]. This was a pamphlet distributed via the Michigan Pneumonia Control Program to every physician in the state in late 1938.

13. Lee Rice, in David R. Sacks and Lee Rice, "Lobar Pneumonia" (Presentation before the Southern Medical Association, November 15–18, 1938), *Southern Medical Journal* 32 (1939): 298.

14. Lionel Whitby, "Chemotherapy of Pneumococcal and Other Infections with 2-(p-aminobenzenesulphonamido) pyridine," *Lancet* 1 (1938): 1210–12. Regarding the history of M&B 693, see John E. Lesch, "The Discovery of M&B 693 (Sulfapyridine)," in *The Inside Story of Medicines: A Symposium,* ed. Gregory J. Higby and Elaine C. Stroud (Madison, Wis.: American Institute of the History of Pharmacy, 1997), 101–19.

15. G. M. Evans and Wilfrid Gaisford, "Treatment of Pneumonia with 2-(p-aminobenzenesulphonamido) pyridine," *Lancet* 2 (1938): 14–19. Evans and Gaisford used no specific therapy among the control group because in Britain pneumonia had never been feared to the extent it had in the United States and antipneumococcal antiserum had never garnered widespread support. See Michael Worboys, "Treatments for Pneumonia in Britain, 1910–1940," in *Medicine and Change: Historical and Sociological Studies of Medical Innovation,* ed. Ilana Löwy (London: John Libbey and Company, Ltd., 1993), 322–29. Conversely, by late 1938, as sulfapyridine implementation faced resistance in the United States, a *Lancet* editor would bemoan the degree to which "therapeutic practice at the present time varies from one country to another" ("Progress in Chemotherapy," *Lancet* 2 (1938): 1245).

16. See Perrin H. Long to Theodore Klumpp, 9/28/38; J. J. Durrett, "Memorandum of Interview with Perrin H. Long, E. Kennerly Marshall," 12/5/38 [both in NDA, Vol. I]; Roderick Heffron to Elliott Robinson, 11/22/38 [Box 203, Folder 1902, Series 18.1 (Grants), RAC].

17. Harry Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (New York: Cambridge University Press, 1997), 71–89. Regarding the Elixir Sulfanilamide fiasco, see also James Harvey Young, "The 'Elixir Sulfanilamide' Disaster," *Emory University Quarterly* 14 (1958): 230–37. As it turned out, the first shipment of sulfapyridine from England to Merck arrived in New York on July 21, 1938, "the very day the FD&C Act was approved" (A. E. Lowe to Chief, Eastern District, 10/7/38 [NDA, Vol. I]).

18. J. J. Durrett, "Memorandum of Interview with Dr. A. R. Dochez, Dr. Cook," 11/28/38 [NDA, Vol. I].

19. Maxwell Finland to Wesley Spink, 2/21/39 [Series II, Subseries A, Box 5, Folder 8, MFP]. See also Maxwell Finland to W. G. Campbell, 2/8/39; Wesley W. Spink to W. G. Campbell, 2/6/39 [both in NDA, Vol. III]; Wesley Spink to Maxwell Finland, 2/15/39 [Series II, Subseries A, Box 5, Folder 8, MFP]. Only two years later, once his wonder drug had been replaced by less visibly toxic derivatives, one of sulfapyridine's leading advocates would admit, in retrospect: "Too often, after a course of sulfapyridine, we have heard the patient say, 'Please, Doc, if I ever get sick again, let me die. That medicine is worse than the disease'" (D. Sergeant Pepper, "Sulfapyridine and Sulfathiazole in the Treatment of Pneumonia" (Presentation before the Ninth District Medical Society, North Carolina, September 26, 1940), *North Carolina Medical Journal* 1 [1940]: 635). See also Lea A. Riely, in J. B. Morey, "The Use of Sulfapyridine and Allied Drugs in the Treatment of Pneumococcus Pneumonia," *Journal of the Oklahoma State Medical Association* 33 (1940): 14. By November of 1943, in discussing the treatment of lobar pneumonia before the New York Academy of Medicine (and by which time sulfadiazine and sulfathiazole had replaced such predecessors), Norman Plummer would, in table form, label sulfanilamide as "Ineffective. Should *not* be used," and sulfapyridine as "Toxic. Should *not* be used" ("The Treatment of Lobar Pneumonia" [Presentation before the New York Academy of Medicine, November 4, 1943], *Bulletin of the New York Academy of Medicine* 20 [1944]: 76, 77).

20. Regarding renal toxicity, Merck was actually the first to report on the potential for sulfapyridine-induced urolithiasis and obstruction; see "Sulfapyridine," undated [NDA, Vol. IV]; Leon Gortler, Interview with Harry John Robinson, 10/9/90 [MA]. For persisting concerns, see Thomas Dublin to Maxwell Finland, 3/5/39 [Series II, Subseries A, Box 2, Folder 12, MFP]. Regarding hematological concerns, see J. J. Durrett, "Memorandum of Interview with Perrin H. Long, E. Kinnerly Marshall," 12/5/38 [NDA, Vol. I]; for persisting concerns, see J. M. Hutcheson, in Kelley and Regan, "Sulfapyridine in the Treatment of Lobar Pneumonia," 359. Concerns regarding the possibility of inducing hepatic toxicity emerged from a single equivocal case finding from Marion Blankenhorn in Cincinnati and developed a life of their own through the medical and scientific rumor mill. See Marion Blankenhorn to J. J. Durrett, 12/23/38; R. W. Weilerstein and John T. Cain, "Memorandum of Interview with Dr. M. H. Dawson," 1/27/39; R. W. Weilerstein and John T. Cain, "Memorandum of Interview with Dr. Evan Evans," 1/27/39 [all in NDA, Vol. II]; Maxwell Finland to Thomas Dublin, 3/10/39 [Series II, Subseries A, Box 2, Folder 12, MFP]. Such diffuse concerns even raised the possibility of legal ramifications for the Commonwealth Fund, which supported pneumonia research with the sulfa drugs in Michigan. See Barbara Quin to C. C. Young, 4/24/39 [Box 203, Folder 1903, Series 18.1 (Grants), RAC]; "Proposed Studies in the Pneumonia Program Carried on by the Michigan Department of Health under a Grant from the Commonwealth Fund," 5/16/39 [Box 203, Folder 1904, Series 18.1 (Grants), RAC]. For similar fears concerning their efforts at pneumonia control in Tennessee, see Barbara S. Quin to W. C. Williams, 6/9/39 [Box 36, Folder 520, Series 12.2, RAC].

21. Marks, *Progress of Experiment,* 83–85. See also J. J. Durrett, "Memorandum of Interview with Perrin H. Long, E. Kennerly Marshall," 12/5/38; J. J. Durrett to W. C. Davison, 12/9/38 [both in NDA, Vol. I].

22. Edward S. Godfrey to Thomas Parran, 12/19/38 [RG443 0425, Box 14]. See also Edward S. Godfrey to Morris Fishbein, 12/22/38; John L. Rice to Thomas Parran, 12/22/38

[both in NDA, Vol. II]. For the earliest expression of concern that the advent of sulfapyridine would mean that "efforts in educating physicians to use specific immune serum will all come to naught," see Hobart Reimann to Maxwell Finland, 11/26/38 [Series II, Subseries A, Box 4, Folder 46, MFP].

23. Thomas Parran to W. G. Campbell, 1/7/39 [NDA, Vol. II]. See also J. J. Durrett, "Memorandum of Interview with Sanford M. Rosenthal and Carl Voegtlin," 12/5/38 [NDA, Vol. I].

24. "Sulfanilamide-Pyridine," *Journal of the American Medical Association* 111 (1938): 2122.

25. "Sulfapyridine," undated [NDA, Vol. IV].

26. Out of 104 investigators surveyed, 54 urged sulfapyridine's immediate release, while 25 opposed it. Others held more qualified positions or remain unaccounted for in this respect. See Ralph Weilerstein, "Evaluation of Sulfapyridine," 2/21/39 [NDA, Vol. III].

27. C. A. Herrmann to Food and Drug Administration, 1/18/39 [NDA, Vol. II].

28. Ibid. (note that the former citation represented Herrmann's paraphrase, the latter reportedly a direct quote). See also Harrison F. Flippin, "Preliminary Report of the Use of Sulfapyridine in the Treatment of Pneumonia," *Bulletin of the New York Academy of Medicine* 15 (1939): 249. For the longstanding links between Merck and the University of Pennsylvania as a clinical testing center, see John P. Swann, *Academic Scientists and the Pharmaceutical Industry: Cooperative Research in Twentieth-Century America* (Baltimore: Johns Hopkins University Press, 1988), 74–79.

29. R. W. Weilerstein, "Memorandum of Interview with Dr. W. S. Tillett," 1/25/39 [NDA, Vol. II].

30. R. W. Weilerstein and John T. Cain, "Memorandum of Interview with Dr. Evan Evans," 1/27/39 [NDA, Vol. II].

31. R. W. Weilerstein, "Memorandum of Interview with Dr. Harold Thomas Hyman," 1/27/39 [NDA, Vol. II].

32. Jesse G. M. Bullowa, as cited in C. A. Herrmann to Food and Drug Administration, 1/18/39 [NDA, Vol. II].

33. R. P. Herwick, "Memorandum of Interview with Lloyd D. Felton," 1/27/39 [NDA, Vol. II]. Felton considered that sulfapyridine, apparently effective for murine type 4 pneumococcal pneumonia, had not yet been shown of value in types 1 and 2, and appeared one-thousandth as effective as serum in type 3. See also note 11 for the continuity between Felton's assessment of sulfanilamide and sulfapyridine.

34. R. P. Herwick and J. Kirk, "Memorandum of Interview with Hobart A. Reimann," 2/4/39 [NDA, Vol. III]. See also Reimann to Maxwell Finland, 3/6/39, wherein Reimann continued to belittle the effects of the "'miracle' drug" in the setting of an obviously mild winter pneumonia season [Series II, Subseries A, Box 4, Folder 46, MFP]. Reimann's own textbook on pneumonia (with a foreword by Rufus Cole) had been published in 1938; see Hobart A. Reimann, *The Pneumonias* (Philadelphia: W. B. Saunders, 1938).

35. David D. Rutstein to W. G. Campbell, 2/7/39 [NDA, Vol. III]. He continued: "As you know, there are many types of pneumococci, each producing distinct types of disease, and we think that special evaluation of the drug should be made for each of these types." Regarding the personal significance of Rutstein's pneumonia control program position in his

evolution as one of the nation's leading preventive medicine experts, see Maxwell Finland and William B. Castle, *The Harvard Medical Unit at Boston City Hospital,* Volume II, *Part I: The Peabody-Minot Tradition, 1915–1950* (Boston: Commonwealth Fund, 1983), 223–24.

36. Maxwell Finland to W. G. Campbell, 2/8/39 [NDA, Vol. III].

37. O. H. Robertson to W. G. Campbell, 2/7/39 [NDA, Vol. III]. The University of Cincinnati's James Ruegsegger concurred: "Its [sulfapyridine's] efficacy as reported in the literature is so non-specific that I fear the wholesale use of this drug will condemn the bacteriological approach to infectious diseases at once, and unwarrantedly so, for there are available at the present time certain therapeutic agents which have been proven beyond a shadow of a doubt to be extremely useful" (J. M. Ruegsegger to W. G. Campbell, 2/21/39); see also David D. Rutstein to W. G. Campbell, 2/7/39 [both in NDA, Vol. III].

38. John T. Cain, R. W. Weilerstein, "Memorandum of Interview with Dr. Jesse G. Bullowa, Dr. Holle," 1/26/39 [NDA, Vol. II].

39. "Sulfapyridine: The New Sulfanilamide Derivative," *Journal of the American Medical Association* 112 (1939): 541. See also Paul Nicholas Leech to W. G. Campbell, 1/26/39 [NDA, Vol. II].

40. Jesse G. M. Bullowa, Norman Plummer, and Maxwell Finland, "Sulfapyridine in the Treatment of Pneumonia," *Journal of the American Medical Association* 112 (1939): 570. The letter appears to have been initially composed by Bullowa before being sent to Plummer and Finland for their commentary and approval. See R. W. Weilerstein and John T. Cain, "Memorandum of Interview with Dr. Norman Plummer, Dr. Henning," 1/27/39 [NDA, Vol. II]. As late as five days before sulfapyridine's eventual release, moreover, the *Saturday Evening Post* quoted the AMA's Morris Fishbein as follows (it is, of course, unclear exactly when he had made the statement): "The old trial-and-error method is yielding to controlled experimentation, and the people are the beneficiaries by increased safety in advancing medical science. In the meantime, manufacturers are developing the product; physicians who can maintain scientific control over its use are studying it; a great contribution to the treatment of many serious diseases is undergoing the travail of being born" ("Sulfanilamide-Cure-All?" *Saturday Evening Post,* 4 March 1939, 24). See also Morris Fishbein to William S. Middleton, 3/2/39; William S. Middleton to Morris Fishbein, 3/11/39 [WMP, Box 8]; Marks, *The Progress of Experiment,* 88.

41. The term "therapeutic rationalist" derives from James Whorton's account of those attempting to inculcate appropriately delimited prescribing of antibiotics in the post–World War II era. See James Whorton, "'Antibiotic Abandon': The Resurgence of Therapeutic Rationalism," in *The History of Antibiotics: A Symposium,* ed. John Parascandola (Madison, Wis.: American Institute of the History of Pharmacy, 1980), 125–36. I would argue that not only were such attempts at therapeutic rationalism anticipated by the debate over the appropriate use of sulfapyridine and serum, but that the most central of the "rationalists" noted by Whorton—Maxwell Finland, Hobart Reimann, and Harry Dowling—first got their rationalist feet wet during the antipneumococcal antiserum debates.

42. R. W. Weilerstein and John T. Cain, "Memorandum of Interview with Dr. D. W. Richards," 1/27/39 [NDA, Vol. II].

43. "Memorandum of Interview at National Institute of Health," 2/27/39 [NDA, Vol. III]. The New York State and New York City Pneumonia Advisory Committees likewise as-

sented to its release, though with faint praise, as related in the State Committee's judgment: "The evidence does not justify the substitution of sulfapyridine for serum therapy in all patients with pneumococcal pneumonia. Further investigations are necessary before it will be possible to state which patients should be treated with serum and which with sulfapyridine" ("Resolution on the Release of the Drug Sulfapyridine by the New York State Committee for Pneumonia Control," accompanying Russell Cecil to Theodore Klumpp, 2/27/39 [NDA, Vol. III]). See also W. D. Sutliff, "Further Statement on the Present Status of Curative Therapy in Pneumonia Prepared for the Advisory Committee on Pneumonia Control at the New York City Department of Health," accompanying same.

44. T. G. Klumpp, "Memorandum of Telephone Conversation with Jesse G. M. Bullowa," 2/25/39 [NDA, Vol. III]. Nevertheless, as late as March 5, 1939, Thomas Dublin had written to Max Finland: "There is still a great deal of unconfirmed rumor about the 'drug.' I hear reports that [Francis] Blake in New Haven is ready to give it up and that it is to be released for sale almost any day" (Thomas Dublin to Maxwell Finland, 3/5/39 [Series II, Subseries A, Box 2, Folder 12, MFP]).

45. Harrison F. Flippin, John S. Lockwood, D. Sergeant Pepper, and Leon Schwartz, "The Treatment of Pneumococcic Pneumonia with Sulfapyridine: A Progress Report on Observations in 100 Cases," *Journal of the American Medical Association* 112 (1939): 532. Contrast such stated caution with Flippin's group's own overwhelming enthusiasm for the drug, in Harrison Flippin to J. M. Carlisle, 11/26/38; I. S. Ravdin to J. M. Carlisle, 11/26/38 [both in NDA, Vol. I].

46. Ralph Weilerstein, "Evaluation of Sulfapyridine," 2/21/39 [NDA, Vol. III].

47. J. D. Ratcliff, "Death to the Killer," *Colliers,* 24 December 1938, 18; "New Drug Is Hailed as Pneumonia Cure," *New York Times,* 18 January 1939, 17; see also, e.g., Stephen J. McDonough, "Sulfapyridine Saved My Life," *Rotarian* 56 (March 1940): 20–22. Nevertheless, and especially in comparison to the widespread acclaim afforded M&B 693 in the British popular press (see John Lesch's forthcoming manuscript on the history of the sulfa drugs), the American popular press remained relatively muted regarding sulfapyridine and was often quick to point to the ongoing potential need for serotherapy as well. See, as rare representatives, J. C. Furman, "Major Miracle," *Ladies Home Journal* 56 (October 1939): 18; Maxine Davis, "The Perennial Plague: An Article on Respiratory Diseases," *Good Housekeeping* 109 (December 1939): 34–35.

48. Jesse G. M. Bullowa, "The Specific Therapy of the Pneumonias: I. The Choice of a Remedy" (Beaumont Foundation Lecture before the Wayne County (Michigan) Medical Society, February 20, 1939), *Journal of the Michigan State Medical Society* 38 (1939): 577.

49. "While [serum has been] effective in many types of pneumococcic pneumonia, it has been costly, frequently unavailable, often tedious and occasionally impossible to give. The advent of sulfapyridine has given us another effective specific agent, and this time one that is comparatively inexpensive, more readily available and more easily administered" (Norman Plummer and Herbert K. Ensworth, "Sulfapyridine in the Treatment of Pneumonia" [Presented on May 17, 1939], *Journal of the American Medical Association* 113 [1939]: 1847). See, similarly, Italo F. Volini, Robert O. Levitt, and N. Louis Campione, "Serum and Drug Therapy in Pneumococcus Pneumonia" (Presentation before the Illinois State Med-

ical Society, May 3, 1939), *Illinois Medical Journal* 76 (1939): 420; James Clement Hart, "The Program for Control of Pneumonia in New Haven," Master of Public Health thesis, Yale University School of Medicine, 1939 [YU, Y12PM15], 87.

50. See D. Sergeant Pepper, Harrison F. Flippin, Leon Schwartz, and John S. Lockwood, "The Results of Sulfapyridine Therapy in 400 Cases of Typed Pneumococcic Pneumonia," *American Journal of Medical Science* 198 (1939): 34; R. W. Weilerstein and John T. Cain, "Memorandum of Interview with Dr. M. H. Dawson," 1/27/39 [NDA, Vol. II].

51. Louis A. Parrella and E. E. Brown, "Sulfapyridine Therapy in Pneumonia" (Presented at the staff meeting of the Central Maine General Hospital, May 1, 1939), *Journal of the Maine Medical Association* 30 (1939): 198, 197.

52. H. Corwin Hinshaw, "Recent Advances in the Management of the Pneumonias," *Medical Clinics of North America* 23 (1939): 955; Edmund Walsh, "Present Day Treatment of Pneumonia (Presentation before the Nebraska State Medical Association, May 4, 1939)," *Nebraska State Medical Journal* 25 (1940): 9; G. S. Bryan, "Reducing the Pneumonia Death Rate" (Presentation before the Medical Association of the State of Alabama, April 19, 1939), *Journal of the Medical Association of the State of Alabama* 9 (1939): 70.

53. Kelley and Regan, "Sulfapyridine in the Treatment of Lobar Pneumonia," 357; Lynn T. Hall, "Sulfanilamide and Allied Azo Dyes in the Treatment of Pneumonia," *Nebraska State Medical Journal* 25 (1940): 13; Ulysses G. Mason and Joseph B. Stocklen, "A Comparative Study of Serum and Sulfapyridine in the Treatment of Lobar Pneumonia" (Presented to the Staff of the Cleveland City Hospital, May 23, 1939), *Ohio State Medical Journal* 36 (1940): 178.

54. Juul C. Nielsen and Louis R. Nash, "Dagenan and Pneumonia" (Read before the Tenth Councilor District, Ingleside, Nebraska, May 25, 1939), *Nebraska State Medical Journal* 24 (1939): 378.

55. "Sulfapyridine," *Journal of the American Medical Association* 112 (1939): 1830.

56. See Pepper, "Sulfapyridine and Sulfathiazole in the Treatment of Pneumonia," 634.

57. Jesse Bullowa, "Serotherapy of the Pneumonias" (Presentation at the Panel Discussion on Pneumonias, American Medical Association, May 16, 1939), *Journal of the American Medical Association* 113 (1939): 1404; Maxwell Finland, "The Treatment of Pneumonia" (Presentation before the Ontario Medical Association, May 30, 1939), *Canadian Medical Association Journal* 41 (1939): 554, 556.

58. Rodney W. Bliss, "Treatment of Pneumonia" (Presentation before the Omaha Douglas County Medical Society, February 28, 1939), *Nebraska State Medical Journal* 24 (1939): 128.

59. Edmond M. Walsh, "Present Day Treatment of Pneumonia" *Nebraska State Medical Journal* 25 (1940): 10.

60. Harold Glascock Jr., "Pneumonia—Home Treatment" (Presentation before the Tri-State Medical Association, February 20–21, 1939), *Southern Medicine and Surgery* 101 (1939): 269, 270. See also Edward A. Birge, "Serum Therapy of Pneumonia," *Wisconsin Medical Journal* 38 (1939): 287, 289. Still, the speaker preceding Glascock, stating that "a worthless patient most always recovers, a useful one frequently succumbs in spite of everything that is done to speed recovery," had demonstrated local variability in advocating cre-

osate carbonate at the expense of (indeed, to avoid the expense of) serotherapy. See R. C. Miller, "Pneumonia—Treatment without Serum in the Family of Low Income," *Southern Medicine and Surgery* 101 (1939): 271.

61. R. V. Williams, "Pneumonia in Rural Communities" (Presentation before the Southern Minnesota Medical Association, September 23, 1940), *Minnesota Medicine* 24 (1941): 79–80. Regarding Cabot and his advocacy of group practice (which would offset individual clinician ignorance), see Hugh Cabot, *The Patient's Dilemma: The Quest for Medical Security in America* (New York: Reynal and Hitchcock, 1940); Jonathan Engel, *Doctors and Reformers: Discussion and Debate over Health Policy, 1925–1950* (Columbia: University of South Carolina Press, 2002), 173–74.

62. James Weatherly to A. C. Baxter, 3/5/39, in "Investigation and Control of Pneumonia, Influenza, and the Common Cold," *Hearings before a Subcommittee of the Committee on Education and Labor, United States Senate, May 6 and 10, 1940* (Washington: U.S. Government Printing Office, 1940), 54.

63. L. D. Thompson, in Plummer and Ensworth, "Sulfapyridine in the Treatment of Pneumonia," 1853–54. Of 121 patients treated with serum, 4.13 percent died, while of 145 patients treated with sulfapyridine 10.3 percent died. Thompson cautioned: "The series are not comparable because the serum treated patients were picked. They consisted of types I, II, V, VII, VIII and XIV but not type III patients, whereas the drug treated patients included a large number of youngsters, that is below 2 years of age, and also a large number of type III patients."

64. Volini, Levitt, and Campione, "Serum and Drug Therapy in Pneumococcus Pneumonia," 420–24. The study instead noted sulfapyridine's known tendency to produce nausea and vomiting.

65. Robert A. Kilduffe, "Recent Advances in the Study of Pneumonia" (Presentation before the Medical Society of New Jersey, June 6–8, 1939), *Journal of the Medical Society of New Jersey* 36 (1939): 648.

66. "Sulfapyridine," *Journal of the American Medical Association,* 1830; for a similar sentiment, see Raymond O. Muether, "Modern Trends in Pneumonia Therapy" (Presentation before the Missouri State Medical Association, April 10–12, 1939), *Journal of the Missouri State Medical Association* 36 (1939): 471.

67. James M. Ruegsegger, Morton Hamburger, and Sarah L. Cockrell, "The Comparative Use of Sulfapyridine and Specific Serum in Pneumococcal Pneumonia," *Ohio State Medical Journal* 36 (1940): 257–61.

68. Regarding the FDA's own emphasis on the number rather than individual intensity of sulfapyridine investigators, see Marks, *Progress of Experiment,* 90, n. 85.

69. Eighty-nine such clinicians were located in New York, 28 in New Jersey. Clinicians from the District of Columbia, Puerto Rico, and Canada were also provided with samples. See "Physicians who have Received Samples of Dagenan (M.B. 693)," 1/25/39 [NDA, Vol. II]. Nevertheless, Merck's leadership, clearly displeased at the delay to sulfapyridine's general release, seems merely to have made the best of what seemed to them the "injustice" of the situation. See R. W. Weilerstein and John T. Cain, "Memorandum of Interview with J. M. Carlisle, Mr. Anderson, Miss Person," 1/25/39 [NDA, Vol. II]. Regarding the contemporary advent of such "seeding" techniques in the 1930s, see Nicolas Rasmussen, "The

Drug Industry and Clinical Research in Interwar America: Three Types of Physician Collaborator," *Bulletin of the History of Medicine* 79 (2005): 63–64; regarding the increasing entrenchment of such techniques within the pharmaceutical industry—most tragically, in the case of thalidomide—see Thomas Maeder, *Adverse Reactions* (New York: William Morrow and Company, 1994), 262. For more recent discussion of the potential conflation of "marketing considerations" and "scientific rationale" in determining clinical trial sample size, see Rabih R. Azar and David D. Waters, "PRINCE's Prospects: Statins, Inflammation, and Coronary Risk," *American Heart Journal* 141 (2001): 883.

70. J. E. Greenstein and Raymond E. Stevens, "The Treatment of Pneumococcus Pneumonia with Sulfapyridine" (Read before the Pawtucket, Rhode Island Medical Association, April 20, 1939), *Rhode Island Medical Journal* 22 (1939): 121; see also R. W. Weilerstein, "Memorandum of Interview with Dr. A. V. St. George," 1/29/39 [NDA, Vol. II].

71. Long and Wood, "Observations upon the Experimental and Clinical Use of Sulfapyridine," 494. To illustrate, two Youngstown (Ohio) investigators would first cautiously praise sulfapyridine and deem it worthy of use "in types for which specific serum for one reason or another is not available or its administration impractical," before later using it, having noted its efficacy, "regardless of the day of the disease and the type of invading organism" (Joseph Rosenfeld and Alex M. Rosenblum, "Sulfapyridine in the Treatment of Pneumonia," *Ohio State Medical Journal* 36 [1940]: 388, 385).

72. R. N. Larimer, "Serum Treatment of Pneumonia" (Presentation before the Iowa State Medical Society, April 25–27, 1939), *Journal of Iowa State Medical Society* 29 (1939): 609.

73. *The Clinical Use of Sulfapyridine in Pneumococcic Pneumonia* (Rahway, N.J.: Merck and Company, 1939), 14–15.

74. Maxwell Finland, "Controlling Clinical Therapeutic Experiments with Specific Serums: With Particular Reference to Antipneumococcus Serums," *New England Journal of Medicine* 225 (1941): 496, 497.

75. Wesley Spink to Maxwell Finland, 8/5/39 [Series II, Subseries A, Box 5, Folder 8, MFP].

76. Maxwell Finland to Wesley Spink, 8/11/39 [Series II, Subseries A, Box 5, Folder 8, MFP]. However, both Spink and Finland retained their reservations at this time, focused more upon efficacy than side effects.

77. Roderick Heffron to Elliott Robinson, 10/3/39 [Box 203, Folder 1904, Series 18.1 (Grants), RAC]. A week earlier Heffron had written: "There seems to be sufficient information now in the literature to clearly indicate that the drug has considerable value and that when used with reasonable care it is not unduly dangerous" (Heffron to Robinson, 9/28/39 [Box 203, Folder 1904, Series 18.1 (Grants), RAC]).

78. In fact, the notion of combination serochemotherapy had been advocated as far back as in Paul Ehrlich's 1913 presentation on chemotherapy before the 17th International Congress of Medicine, at which time, paradigmatically, he had advocated such combination therapy for the treatment of pneumonia itself (using methylhydrocupreine as the chemotherapeutic agent)! See Paul Ehrlich, "Chemotherapy," in *The Collected Papers of Paul Ehrlich,* Volume 3: *Chemotherapy,* ed. F. Himmelweit (New York: Pergamon Press, 1960), 514–15.

79. Alexander Fleming, "The Antibacterial Action *in Vitro* of 2-(p-aminobenzenesulphonamido) pyridine on Pneumococci and Streptococci," *Lancet* 2 (1938): 74–78. Again, the military metaphors sustaining advocacy of combination serochemotherapy had their own origins in Ehrlich's previously cited presentation on chemotherapeutic "tactics," in which he had emphasized that through combination therapy, "a simultaneous and varied attack is directed at the parasites, in accordance with the military maxim, march in detachments, fight as a unit" (Ehrlich, "Chemotherapy," 512, 514).

80. C. A. Herrmann to Food and Drug Administration, 1/18/39 [NDA, Vol. II]; see also Bullowa, "The Specific Therapy of the Pneumonias. I. The Choice of a Remedy," 566–67. As early as 1937, Bullowa had apparently been clinically testing the combination of sulfanilamide and serotherapy for type 3 pneumococcal pneumonia; and in August of 1938 Osgood had first published the finding that in marrow cultures, sulfanilamide and antiserum were more effective against the pneumococcus than was serum alone. See Thomas Parran to Jesse Bullowa, 12/9/37 [RG443 0425, Box 14]; Edwin E. Osgood, "A Comparative Study of the Effects of Sulfanilamide and Antipneumococcus Serum on the Course of Experimental Pneumococcic Infections," *Archives of Internal Medicine* 62 (1938): 181–98.

81. Colin MacLeod, "Chemotherapy of Pneumococcic Pneumonia," *Journal of the American Medical Association* 113 (1939): 1407. As a gauge of contemporary interest in the matter, in a fascinating notation, J. T. Tripp, associate director of the Michigan State Department of Health's Bureau of Laboratories, wrote to Barbara Quin of the Commonwealth Fund of Arthur W. Frisch, a clinician (to be discussed in greater detail in chapter 7) working under the auspices of the program at the Detroit Receiving Hospital: "Has some very definite ideas as to a method of preparing a new chemotherapeutic agent. Essentially this is a coupling of sulfanilamide to pneumococcal antibody" (J. T. Tripp to Barbara S. Quin, 4/27/39 [Box 203, Folder 1903, Series 18.1 (Grants), RAC]). At the same time, in Britain, Alexander Fleming supported the "synergic" combined use of active vaccination with M&B 693. See Ian H. MacLean, Keith B. Rogers, and Alexander Fleming, "M&B 693 and Pneumococcus," *Lancet* 1 (1939): 564.

82. See, for example, R. W. Weilerstein, "Memorandum of Interview with Dr. W. S. Tillett," 1/25/39; R. W. Weilerstein and John T. Cain, "Memorandum of Interview with Dr. Norman Plummer, Dr. Henning," 1/27/39 [both in NDA, Vol. II]; D. T. Smith, in Kelley and Regan, "Sulfapyridine in the Treatment of Lobar Pneumonia," 359; Muether, "Modern Trends in Pneumonia," 473; Larimer, "Serum Treatment of Pneumonia," 609; Robert H. Williams and Hugh J. Morgan, "The Treatment with Sulfapyridine of Fifty Patients with Pneumococcic Lobar Pneumonia," *Southern Medical Journal* 32 (1939): 607.

83. Finland, "The Treatment of Pneumonia," 560. See also F. E. Schmidt, "The Present Status of Antipneumococcus Serum and Sulfapyridine in the 'Management of the Pneumonias,'" *Journal of the Arkansas Medical Society* 36 (1939): 91. Continuing to invoke an emergency ethos, Schmidt would warn: "Remember hesitant methods do not save patients, therefore, again: Combined serum and sulfapyridine and **both early**." Self-styled therapeutic rationalist Hobart Reimann, working with Pennsylvania's State Pneumonia Committee, would apparently feel strongly enough about the merits of combination therapy in saving lives to encourage its widespread use and "cloud the picture insofar as the true value of the drug in pneumonia" was concerned. In Roderick Heffron to Elliott Robinson, 10/5/

39 [Box 203, Folder 1904, Series 18.1 (Grants), RAC]. Again, the overall emphasis on both the potentially synergistic and the toxicity-limiting application of combination therapy could be traced to Paul Ehrlich's lecture on chemotherapy from over two decades prior (Ehrlich, "Chemotherapy," 515).

84. Francis G. Blake and James W. Haviland, "Sulfapyridine in the Treatment of Pneumonia" (Presentation before the Connecticut State Medical Society, May 25 and 26, 1939), *Journal of the Connecticut State Medical Society* 3 (1939): 671. Such a stance represented a shift from Blake's more generally pro-combination therapy leanings of nearly four months earlier, as stated in T. G. Klumpp, "Memorandum of Interview with Dr. Francis G. Blake," 2/2/39 [NDA, Vol. II].

85. Volini et. al, "Serum and Drug Therapy in Pneumococcus Pneumonia," 424.

86. Charles A. Janeway and Paul B. Beeson, "The Treatment of Pneumococcal Pneumonia: With Special Reference to the Use of Sulfathiazole, Intramuscular Serum, the Francis Test and Histaminase," *New England Journal of Medicine* 224 (1941): 593. Janeway and Beeson clearly located their therapeutic coordinates in lumping Maxwell Finland and Harrison Flippin together as only advocating the addition of serum in selected cases.

87. John W. Brown to Maxwell Finland, 2/9/41 [Series II, Subseries A, Box 1, Folder 48, MFP]. While Italo Volini's group at Cook County Hospital and Loyola University stated their opposition to combination therapy, a second group at Cook County Hospital, and Northwestern University Medical School, from January to May 1939, evolved from emphasizing monotherapy to combination therapy "under certain conditions." See William L. Winters, Paul S. Rhoads, Wayne W. Fox, and Reno Rosi, "The Treatment of Pneumococcic Pneumonia with Sulfapyridine," *Annals of Internal Medicine* 14 (1941): 1836. Hopkins' Perrin Long himself, who had greatly impressed the FDA's evaluators with his willingness, by March of 1939, to have "given up the use of serum," evolved towards the use of combination therapy for nearly a quarter of his patients. Compare Perrin Long to J. J. Durrett, 3/1/39 [NDA, Vol. III]; Long and Wood, "Observations upon the Experimental and Clinical Use of Sulfapyridine," 502–4; Perrin H. Long and James W. Haviland, "The Problem of Pneumonia with Reference to Chemo- and Sero-Therapy," *Annals of Internal Medicine* 14 (1940): 1045.

88. Roy E. Thomas, "Evaluation of the Newer Therapy in the Pneumonias," *California and Western Medicine* 54 (1941): 106.

89. Lawrence D. Thompson, Luther L. Terry, and Joseph C. Edwards, "Pneumococcal Pneumonia: Observations upon the Incidence and Therapy in St. Louis Area, 1939–1940," *Journal of the Missouri Medical Association* 37 (1940): 465. For earlier thoughts on the matter, see Roderick Heffron, "Michigan Department of Health-Pneumonia Study," 5/19/39 [Box 203, Folder 1904, Series 18.1 (Grants), RAC]. See also James W. Haviland, "Type I Pneumococcal Pneumonia: Clinico-Immunological Studies with Special Reference to the Rationale of Combined Serum and Drug Therapy," *Bulletin of the Johns Hopkins Hospital* 68 (1941): 33.

90. T. J. Charlton, in J. Fletcher Hanson, "Treatment of Pneumonia in Adults with Sulfapyridine" (Presentation before the Medical Association of Georgia, April 25, 1940), *Journal of the Medical Association of Georgia* 29 (1940): 571. See also James Ruegsegger, "The Treatment of Pneumonia," *Ohio State Medical Journal* 36 (1940): 148; Karl B. Hanson and

Ralph P. Panzer, "Lobar Pneumonia: A Review of 147 Cases" (Presentation before the Chattahoochee Valley Medical Society, July 9, 1940), *Journal of the Florida Medical Association* 27 (1941): 336.

91. W. G. Reddick, "Treatment of Pneumonia with Sulfanilamide, Sulfapyridine and its Allied Compounds" (Presentation before the State Medical Association of Texas, May 15, 1940), *Texas State Medical Journal* 36 (1940): 354, 356.

92. Of course, as in the field as a whole, such decisions derived from ongoing reevaluations, often problematizing the very capacity of leading clinicians to offer definitive recommendations. As Roderick Heffron wrote to Elliott Robinson of the stance of the New York program by late 1939: "At the Microbiological Congress I talked with one of the men connected with the New York State Pneumonia Program and also with [Wheelan] Sutliff, who is running the New York City program, and asked them what stand they were taking on the use of sulfapyridine versus serum. In both instances I find they have carefully hedged on the matter and I think they are probably wise in doing so at the present time. . . . Until we know more about the limitations and usefulness of the drug I do not see how anyone can be more definite than this when giving advice on a large scale such as is necessary." Robinson, from the Massachusetts program, concurred: "It is perhaps not very helpful but somewhat comforting to know that others are in doubt as to what to recommend in regard to sulfapyridine. . . . I think we all feel that current practice may change two or three times in the course of the winter and, therefore, it would be foolish to have printed directions made" (Roderick Heffron to Elliott Robinson, 9/20/39; Elliott Robinson to Roderick Heffron, 9/21/39 [both in Box 203, Folder 1904, Series 18.1 (Grants), RAC]). Over a year later, New York's pneumonia control experts would continue to accompany their recommendations with the caveat: "Due to the rapid development of both serum and chemotherapy, the following discussion regarding their relative merits must be considered as somewhat tentative, and changes in point of view may be indicated as more information becomes available" (Edward S. Rogers, David D. Rutstein, and Alexander Langmuir, "Specific Treatment of Pneumonia: With Special Reference to Chemotherapy and Antipneumococcus Serum," *New York State Journal of Medicine* 41 [1941], 111).

93. The same could be said for the state of Iowa, where during the 1939–40 pneumonia season, nearly two-thirds (185/295) of types I and II pneumococcal pneumonia cases, themselves representing half of all reported cases, received combination therapy (State of Iowa, *Report of the State Department of Health for the Biennial Period Ending June 30, 1940,* 29–31).

94. Irving Applebaum, "The Chemotherapy of the Pneumonias (Read before the Hunterdon County Medical Society, January 23, 1940)," *Diseases of the Chest* 6 (1940): 116. New Jersey's Department of Health provided serum only to those "financially unable to pay for the material," with physicians required to attest to such financial status, with such attestations subject to review, and with violations thereby uncovered resulting in the preclusion of further serum provision to offending physicians. See *61st Annual Report of the Department of Health of the State of New Jersey, 1938* (MacCrellish and Quigley Company, 1939), 37–38. For Merck, see *63rd Annual Report of the Department of Health of the State of New Jersey, 1940* (MacCrellish and Quigley Company, 1941), 42.

95. *New Mexico Health Officer* 9 (1941): 108.

96. The four respective counties were Jackson (16/64), DeKalb (17/22), Peoria (52/204), and Rock Island (84/112). In *25th Annual Report of the [Illinois] Department of Public Health, July 1, 1941 to June 30, 1942*, 71–73.

97. Ibid., 59, 69.

98. "Comparative Value of Serum Therapy and Chemotherapy in Pneumococcic Pneumonia," *Journal of the American Medical Association* 114 (1940): 663. See also Russell L. Cecil, Edgar A. Lawrence, and Edward Tolstoi, "Sulfapyridine in the Treatment of Pneumonia," *New York State Journal of Medicine* 40 (1940): 493.

99. "I doubt whether any conscientious physician would deny a pneumonia victim the chance of halving the mortality of his disease simply because adequate control was impossible" (O. P. J. Falk, "Modern Treatment of Pneumonia: With Discussion of Atypical Types," *Journal of the Missouri Medical Association* 37 [1940]: 13). See also W. G. Reddick, "Sulfapyridine in the Treatment of Pneumonia" (Presentation before the Southern Medical Association, November 21–24, 1939), *Southern Medical Journal* 33 (1940): 418. For a contrary view from Reddick's state of Texas, see Victor E. Schulze, "Sulfapyridine in Pneumonia," *Southern Medical Journal* 33 (1940): 211.

100. Yale Kneeland, "The Treatment of Pneumonia with Sulfapyridine," *Medical Clinics of North America* 24 (1940): 645–46.

101. Indeed, published modus operandi began to present the first hints of serum's final role: as a backup to the sulfa drugs. Even among the sulfa drugs' most ardent supporters, such a role for serum among those patients unable to tolerate the sulfa drugs secondary to contraindications or side effects had long been noted. See K. G. Kohlstaedt and Irvine H. Page, "The Treatment of Pneumococcic Pneumonia with Sulfapyridine," *Journal of the Indiana State Medical Association* 32 (1939): 273. Of course, in an era of therapeutic variability, some practitioners instead used serum up front, with sulfapyridine as a backup. See William H. Lohman and Robert M. Bogue, "Treatment of Pneumonia with Sulfapyridine," *Brooklyn Hospital Journal* 1 (1939): 122; George Taplin, "Serum Treatment of Pneumococcic Pneumonia," *Journal of the American Medical Association* 115 (1940): 1679. Furthermore, over time, clinicians avoiding up-front combination therapy still debated when to add serum as rescue therapy to those pneumonia patients succumbing in the face of the apparent failure of the sulfa drugs.

102. Maxwell Finland, "Treatment of Pneumonia with Sulfapyridine and Specific Serum" (Presentation before the Michigan State Medical Society, September 22, 1939), *Journal of the Michigan State Medical Society* 39 (1940): 317.

103. Maxwell Finland, Francis C. Lowell, and William C. Spring, "Clinical and Laboratory Studies on the Use of Serum and Sulfapyridine in the Treatment of the Pneumococcal Pneumonias," *New England Journal of Medicine* 222 (1940): 747. Finland and his colleagues also seem to have eliminated pregnancy as a category mandating combination therapy. Nevertheless, they maintained multilobar and type III pneumonias as indications for combination therapy, while adding to consideration type II and "possibly" type V pneumonias. Moreover, they continued to advocate serum alone for certain cases (i.e., in patients seen early in the course of pneumonia, in which the use of efficacious serotherapy would eliminate the need for the potentially toxic sulfa drugs).

104. One clinician, despite agreeing that the pro-combination advocates might be right

in their continued championing of combination therapy for particular patient subgroups, nevertheless remarked: "The death struggle of the proponents of serum is rather pathetic. The fact is apparent that chemotherapy has accomplished in a short time what they have tried for more than a quarter of a century, without success, to accomplish. We cheer them for their efforts, for their efforts were noble" (Conley H. Sanford, "Specific Treatment of Pneumonia" [Presentation before the Memphis and Shelby County Medical Society, January 21, 1941], *Memphis Medical Journal* 16 [1941]: 31).

105. Kneeland, "The Treatment of Pneumonia with Sulfapyridine," 646.

106. J. O. Manier, "Sulfanilamide and its Compounds: Their Uses in Medicine (Presentation before the Tennessee State Medical Association, April 9–11, 1940)," *Journal of the Tennessee Medical Association* 33 (1940): 298; Francis G. Blake, "The Treatment of Pneumococcal Pneumonia" (Presentation before the Massachusetts Medical Society, May 21, 1940) *New England Journal of Medicine* 223 (1940): 667.

107. Long and Haviland, "The Problem of Pneumonia with Reference to Chemo- and Sero-Therapy," 1049.

108. Hobart A. Reimann, "Pneumococcal and 'Virus' Pneumonia" (Presentation before the New York Academy of Medicine, October 17, 1940), *Bulletin of the New York Academy of Medicine* 17 (1941): 190; Maxwell Finland to Wesley Spink, 12/2/40 [Series II, Subseries A, Box 5, Folder 8, MFP]. Under Harry Dowling's care at Gallinger Municipal Hospital, 16/115 patients treated with sulfadiazine from December of 1940 until June of 1941 would receive serum; while under Curtis Garvin's care at Cleveland City Hospital from July of 1940 until June of 1941, 23/85 patients treated with sulfapyridine or sulfathiazole would receive serum. See Harry F. Dowling, Clarence R. Hartman, Samuel J. Sugar, and Harry A. Feldman, "The Treatment of Pneumococcic Pneumonia with Sulfadiazine," *Journal of the American Medical Association* 117 (1941): 824; Curtis F. Garvin, "Sulfathiazole and Sulfapyridine in the Treatment of Pneumococcic Pneumonia," *Ohio State Medical Journal* 38 (1942): 231.

109. R. O. Canada, "Sulfapyridine Treatment of Pneumonia: Employed Alone and Combined with Serum," *United States Naval Bulletin* 39 (1941): 108–14. Canada had administered serum "to all cases in which a pneumococcus type could be established," unless the patient was already recovering via sulfapyridine alone. The mean age of his patients was 21.2 years, with a range from 2–36 years. The only death in the entire study was actually ascribed to sulfa-induced renal toxicity.

110. Harry F. Dowling, Theodore J. Abernethy, and Clarence R. Hartman, "Should Serum be Used in Addition to Sulfapyridine in the Treatment of Pneumococcic Pneumonia?" *Journal of the American Medical Association* 115 (1940): 2125–28. Bullowa likewise attempted to use a post hoc analysis to justify combination therapy. Having alternated over four hundred patients to receive treatment with serum alone, sulfapyridine, or combination therapy, and having derived absolute mortality rates of 17.3 percent among the serum-treated, 8.1 percent among the sulfapyridine-treated, and 11.2 percent among the combination treated, Bullowa declared that the lowest mortality rate among all patients was achieved among those receiving combination therapy in "early treated cases (1 to 4 days)." Such unconvincing clinical data, not surprisingly, was tucked into the back of a larger article concerning the response of pneumococcus-infected marrow cultures to such treatments. See

Jesse G. M. Bullowa, Edwin E. Osgood, Samuel C. Bukantz, and Inez E. Brownlee, "The Effect of Sulfapyridine Alone and with Serum on Pneumococcic Pneumonia and on Pneumococcus-Infected Marrow Cultures," *American Journal of Medical Science* 199 (1940): 373–76.

111. Norman Plummer, James Liebmann, Saul Solomon, W. H. Kammerer, Mennasch Kalkstein, and Herbert K. Ensworth, "Chemotherapy versus Combined Chemotherapy and Serum in the Treatment of Pneumonia: A Study of 607 Alternated Cases," *Journal of the American Medical Association* 116 (1941): 2366–71. Likewise, they found that combination therapy was no better than chemotherapy alone in either "early"-treated (first three days) or "late"-treated cases.

112. D. C. Stahle, "A Clinical Analysis of Fifteen Thousand Cases of Pneumonia: An Evaluation of the Effectiveness of Various Therapeutic Agents," *Journal of the American Medical Association* 118 (1942): 440–47. Twenty-four percent of the patients had been treated at home.

113. Plummer et. al., "Chemotherapy versus Combined Chemotherapy and Serum," 2370; Stahle, "A Clinical Analysis of Fifteen Thousand Cases of Pneumonia," 446; William S. Tillett, "Specific Antipneumococcal Immunity in Relation to the Outcome of Chemotherapy in Pneumonia" (Read on May 6, 1941), *Transactions of the Association of American Physicians* 56 (1941): 147–51.

114. Russell Cecil, in Tillett, "Specific Antipneumococcal Immunity," 151. Cecil, it should be noted, was one of the members of a Committee for Pneumonia Investigation helping to oversee Plummer's study.

115. Plummer et al., "Chemotherapy versus Combined Chemotherapy and Serum," 2370.

116. Stahle, "Clinical Analysis of Fifteen Thousand Cases of Pneumonia," 446.

117. Bullowa, in ibid., 446; Finland, "Controlling Clinical Therapeutic Experiments with Specific Serums: With Particular Reference to Antipneumococcus Serums," 495–506. When the pro-combination therapy Illinois Pneumonia Control Officer presented strikingly similar retrospective, uncontrolled findings to Stahle's a year later, he likewise echoed Bullowa in arguing for the assumed more dire status of those patients considered necessitating combination therapy. See Reno Rosi, O. K. Sagen, and E. A. Prange, "Pneumonia in Illinois: 1938–1941," *Journal of the American Medical Association* 119 (1942): 1014.

118. Bullowa, in Stahle, "Clinical Analysis of Fifteen Thousand Cases of Pneumonia," 447.

119. Edwin J. Simons, "Pneumonia in a Rural Practice: Its Incidence and Mortality," *Journal of the American Medical Association* 119 (1942): 622.

120. "Serum versus Chemotherapy in Pneumococcus Infections," *North Carolina Medical Journal* 2 (1941): 309.

121. An editorial published in the *Journal of the Indiana State Medical Association* the same month as was the aforementioned North Carolina editorial would relate: "It is the consensus that the use of combined serum gives the most satisfactory results." It is unclear if this was written prior to the publication of Plummer's study. See "Pneumococcal Pneumonia," *Journal of the Indiana State Medical Association* 34 (1941): 311.

122. F. T. Billings Jr., and W. Barry Wood Jr., "Studies on Sulfadiazine. III: The Use of

Sulfadiazine in the Treatment of Pneumococcal Pneumonia," *Bulletin of the Johns Hopkins Hospital* 69 (1941): 326. For the persistence of combination therapy in Baltimore at the time, see Harry G. Wood, "Present-Day Treatment of Pneumonia," *Minnesota Medicine* 25 (1942): 25.

123. Harry F. Dowling, "Problems Arising in the Chemotherapy of Pneumonia and Meningitis," *Medical Annals of the District of Columbia* 10 (1941): 466–67.

124. Later in the paper, he attempted a clarification of such groups to entail "patients over forty years of age who have positive blood cultures or extensive pulmonary involvement [. . . and possibly . . .] pregnant or recently parturient women with a severe infection" (Maxwell Finland, "Present-Day Specific Treatment of Pneumonia," *Medical Clinics of North America* 25 [1941]: 1199, 1209).

125. Roderick Heffron to Maxwell Finland, 3/10/42 [Series II, Subseries A, Box 2, Folder 41, MFP].

126. Ibid.

127. From June to December of 1941, 707/1947 specifically treated patients (excluding the 17 patients who still received serotherapy alone) received combination therapy, while from January to June of 1942, 1044/2878 such patients (excluding 45 who received serum alone) were so treated (*25th Annual Report of the [Illinois] Department of Public Health, July 1, 1941–June 30, 1942,* 64). Similarly, in North Dakota (with its own surprisingly extensive pneumonia control program), where from 10–15 percent of specifically treated patients received combination therapy from 1940 to 1941, "a large portion of the cases received both serum and drug" from 1942–1943 (*North Dakota State Department of Health, 27th Biennial Report, July 1, 1940 to June 30, 1942,* 17–18; *North Dakota State Department of Health, 28th Biennial Report, July 1, 1942 to June 30, 1944,* 22–23).

128. Chester S. Keefer, in Kelley, "Sulfapyridine and Sulfathiazole Therapy in Lobar Pneumonia," *Southern Medical Journal* 35 (1942): 209. Continued Keefer: "It is our impression, in Boston at least, where we see quite a few patients with pneumonia every winter, that better results can be obtained, as far as mortality statistics are concerned, in patients who are over 40 and who have bacteremia if they receive combination treatment. So our general policy at the present time has been to use the combined treatment in patients who have the poorest outlook." Regarding Keefer, see Maxwell Finland, *The Harvard Medical Unit at Boston City Hospital,* Volume I: *History of the Thorndike Memorial Laboratory and the Harvard Medical Services from their Founding until 1974* (Boston: Commonwealth Fund, 1982), 319–23, 706–7; Gladys L. Hobby, *Penicillin: Meeting the Challenge* (New Haven, Conn.: Yale University Press, 1985), 141–51.

129. Kelley, "Sulfapyridine and Sulfathiazole Therapy in Lobar Pneumonia," 210.

130. Ibid., 208–10. See also Arthur W. Frisch, Alvin E. Price, and Gordon B. Myers, "Pneumococcic Pneumonia: The Selection and Control of Serum and Chemotherapy by Sputum Examination," *American Journal of Medical Science* 205 (1943): 778. Frisch and his colleagues actually argued against the routine use of backup serotherapy in their paper, advocating its usage only in the 2 percent of cases they found to be drug-resistant.

131. Norman Plummer, "The Treatment of Pneumonia" (Presentation before the Indiana State Medical Association, September 30, 1942), *Journal of the Indiana State Medical Society* 35 (1942): 611. He continued by damning serotherapy with faint praise: "In spite of

this experience, because of my acceptance of the past and theoretical value of serum, I am not ready fully to discard it."

132. Osler L. Peterson and Maxwell Finland, "Modern Treatment of Pneumonia," *Medical Clinics of North America* 27 (1943): 1302.

133. Nathan H. Shackman and Jesse G. M. Bullowa, "Sulfadiazine Administered Alone and with Antipneumococcus Serum in the Treatment of Pneumococcic Pneumonia," *Archives of Internal Medicine* 72 (1943): 344.

134. Compare, for example, the calls from the pro-combination advocates from the Illinois Pneumonia Control Program with those from Flippin's pro-monotherapy group: Rosi et al., "Pneumonia in Illinois: 1938–1941," 1014; Harrison F. Flippin, Leon Schwartz, and Albert H. Domm, "Modern Treatment of Pneumococcic Pneumonia" (Read at the 93rd meeting of the American Medical Association, June 11, 1942), *Journal of the American Medical Association* 121 (1943): 235. For the persistence of contemporary debate and variability, compare three papers from a "Symposium on Pneumonia" of the Omaha Mid-West Clinical Society, October 1943: Lynn T. Hall, "Is the Incidence, Virulence and Mortality of Pneumonia on the Decline?" *Journal of the Omaha Mid-West Clinical Society* 5 (1944): 47; John F. Gardiner, "The Treatment of Pneumonia," *Journal of the Omaha Mid-West Clinical Society* 5 (1944): 58; Maine C. Andersen, "In View of Present Day Treatment, Are Typing and Serums Necessary?" *Journal of the Omaha Mid-West Clinical Society* 5 (1944): 48.

135. Cole had retired from the Hospital of the Rockefeller Institute in 1937 and was more open-minded about the potential for the chemotherapeutic approach to pneumonia than has been conventionally described. See Rufus Cole to G. M. Mackenzie, 2/1/39 [RCP]. Bullowa, perhaps most importantly, died in 1943. Finland, as has been pointed out by F. Marc Laforce, would become an international authority on infectious diseases broadly, but he increasingly turned his attention away from the pneumococcus by the end of the war. In Laforce, "The Pneumococcus and Pneumococcal Infection," lecture at the Maxwell Finland Centennial Celebration, 3/16/02. See also Maxwell Finland to John W. Brown, 9/12/46 [Series II, Subseries A, Box 1, Folder 48, MFP]; Elias Straus to Maxwell Finland, 5/22/46 [Series II, Subseries A, Box 5, Folder 19, MFP]. Cecil and Plummer, of course, had been the most visible remaining serum advocates in the pre-sulfapyridine era. Lederle's own transfer of attention from serum to sulfapyridine will be discussed in chapter 7.

136. *Internal Medicine in World War II,* Volume II: *Infectious Diseases,* ed. W. Paul Havens Jr., John Boyd Coates Jr. (Washington, D.C.: Office of the Surgeon General, Department of the Army, 1963), 30.

137. Hobart A. Reimann, "An Acute Infection of the Respiratory Tract with Atypical Pneumonia: A Disease Entity Probably Caused by a Filterable Virus," *Journal of the American Medical Association* 111 (1938): 2377–84. Not surprisingly, "atypical pneumonia" has had its own interesting and convoluted conceptual history, complementary to the history of pneumonia itself. By the turn of the twentieth century, the term was used in one prominent instance to refer to non-pneumococcal pneumonias, though it still seems to have carried symptomatic and anatomic connotations (one clinician wrote to Cole in 1917 of "atypical" type II pneumonias), to the point that Flexner queried Cole on the utility of the term itself. Despite Cole's own attempt to reclassify pneumonia along microbiological lines, he still favored the term "atypical" by the 1930s (perhaps in an effort to avoid anatomical fo-

cus) to describe those pneumonias clinically distinct from typical lobar pneumonia. He made a convert in Reimann, who became the leading authority on atypical pneumonia by the late 1930s and early 1940s. See Robert Bruce Preble, *Pneumonia and Pneumococcus Infections* (Chicago: C. J. Head and Company, 1905), 175–77; Edgar G. Stillman to Rufus Cole, 11/10/17; Simon Flexner to Rufus Cole, 9/13/19; Rufus Cole to Hobart Reimann, 10/10/30; Hobart Reimann to Rufus Cole, 12/18/37 [all in RCP]; Russell Cecil to Maxwell Finland, 10/21/36 [Series II, Subseries A, Box 1, Folder 56, MFP].

138. Hobart A. Reimann, "The Changing Nature of Pneumonia," *Annals of Internal Medicine* 33 (1950): 1250–51. By the end of World War II pneumococcal pneumonia would again apparently reclaim its position as the most common form of pneumonia. See Hobart A. Reimann, "The Viral Pneumonias and Pneumonias of Probable Viral Origin," *Medicine* 26 (1947): 184.

139. Ibid. Such a shift in attention would be evident in *Index Medicus*—formerly overrun with articles on the use of the sulfa drugs for pneumonia—by the first half of 1943, with articles in American journals concerning "atypical" or "viral" pneumonia exceeding those concerning the therapy of pneumonia itself. See also Maxwell Finland to John W. Brown, 3/3/42 [Series II, Subseries A, Box 1, Folder 48, MFP].

140. William S. Tillett, Margaret J. Cambier, and James E. McCormack, "The Treatment of Lobar Pneumonia and Pneumococcal Empyema with Penicillin" (Presentation before the New York Academy of Medicine, November 4, 1943), *Bulletin of the New York Academy of Medicine* 20 (1944): 142–78. Tillett's findings had been hinted at three months earlier in *JAMA* with the Committee on Chemotherapeutic and Other Agents' report of the first 500 "cases of various infections" treated with penicillin. See Chester S. Keefer, Francis G. Blake, E. Kennerly Marshall Jr., John S. Lockwood, and W. Barry Wood, "Penicillin in the Treatment of Infections: A Report of 500 Cases," *Journal of the American Medical Association* 122 (1943): 1221.

141. Norman Plummer, "The Treatment of Lobar Pneumonia" (Presentation before the New York Academy of Medicine, November 4, 1943), *Bulletin of the New York Academy of Medicine* 20 (1944): 76. Tillett had, in early 1943, reported on two cases of pneumonia that required the successful use of antiserum in the setting of sulfonamide resistance but in which the responsible pneumococci were likewise found in mice to be penicillin-sensitive. See William S. Tillett, Margaret J. Cambier, and William H. Harris Jr., "Sulfonamide-Fast Pneumococci: A Clinical Report of Two Cases of Pneumonia Together with Experimental Studies of the Effectiveness of Penicillin and Tyrothricin against Sulfonamide-Resistant Strains," *Journal of Clinical Investigation* 22 (1943): 249–55. As an intriguing legacy of the combination ethos, antipneumococcal combination therapy with sulfa drug and penicillin apparently became prominent by the late 1940s; see Charles H. Rammelkamp to Maxwell Finland, 4/3/47 [Series II, Subseries A, Box 4, Folder 39, MFP].

142. *Internal Medicine in World War II*, 30.

143. Bernando A. Samper and Maxwell Finland, "Present Day Specific Treatment of the Pneumonias," *Medical Clinics of North America* 28 (1944): 1080. In his study of 54 "rather severe" cases of pneumonia treated with penicillin (in 17 cases as backup to sulfa therapy, in 37 cases as primary treatment) from March to December of 1944, serotherapy was not used once. See Manson Meads, H. William Harris, and Maxwell Finland, "Treatment of

Pneumococcal Pneumonia with Penicillin," *New England Journal of Medicine* 232 (1945): 747–55.

144. The dismissal of serotherapy was apparently based on its having been "dropped by the Scope Committee of the U.S. Pharmacopeia as having no therapeutic value." In Arthur C. De Graff (chairman, Bellevue Hospital Committee on Drugs and Formulary) to William S. Tillett, 10/13/44 ["Drugs and Formulary Committee Minutes," BHR].

145. "Statement of W. G. Malcolm," United States Congress, Senate Committee on the Judiciary, Subcommittee on Antitrust and Monopoly, *Administered Prices, Part 24: Administered Prices in the Drug Industry (Antibiotics),* 86th Congress, 2nd session, 1960, 13635.

146. State of New York, *66th Annual Report of the State Department of Health,* 1945, I:146.

147. The latest published recommendation I have found by an American clinician for serotherapy's continued usage as a component of combination therapy dates to 1947. Ironically, the clinician, Rush College of Medicine's Frank B. Kelly, practiced at Cook County Hospital. See Kelly, "The Treatment of Pneumonia," *Medical Clinics of North America* 31 (1947): 56. For the commercial consideration of the reintroduction of (human-derived) antipneumococcal antiserum three decades later, see Myron W. Fisher to Maxwell Finland, 9/14/78; Myron W. Fisher to Maxwell Finland, 9/22/78 [Series II, Subseries A, Box 4, Folder 20, MFP].

Chapter 7. A "Modern" Revolution

1. Harry Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (New York: Cambridge University Press, 1997), 6.

2. Ibid., 129–35.

3. Ibid., 116–17.

4. Ibid., 136–63.

5. Ibid., 145–46.

6. Ibid., 213–14. Marks continues: "Following the Second World War, therapeutic reformers increasingly put their faith in methods, not men, engendering all the dilemmas of a rationalist polity discussed here" (236).

7. Barron H. Lerner, "Scientific Evidence versus Therapeutic Demand," *Annals of Internal Medicine* 115 (1991): 319. For internal citation, see Harold Edgar and David J. Rothman, "New Rules for New Drugs: The Challenge of AIDS to the Regulatory Process," *Milbank Quarterly* 68 Suppl 1(1990): 139. James Whorton, in his discussion of "antibiotic abandon" in the immediate decades following World War II, likewise concludes with the optimistic premise that a "resurgence of therapeutic rationalism" was thereby engendered ("'Antibiotic Abandon': The Resurgence of Therapeutic Rationalism," in *The History of Antibiotics: A Symposium,* ed. John Parascandola [Madison, Wis.: American Institute of the History of Pharmacy, 1980], 125–36). Harry Marks has previously drawn attention to Whorton's own neglect of pre–World War II concerns with therapeutic rationalism in *The Progress of Experiment,* 150–58.

8. Lester J. Evans, "Subject: Lobar Pneumonia Manuscript by Heffron," 6/22/34 [Box 184, Folder 1732, Series 18.1 (Grants), RAC]. Eventually, Heffron would offer two manu-

scripts: a how-to guide (which would itself evolve over subsequent editions) for the "average doctor" and public health departments, and an encyclopedic treatise that has remained a classic more than six decades later. See Frederick Lord and Roderick Heffron, *Lobar Pneumonia and Serum Therapy: With Special Reference to the Massachusetts Pneumonia Study* (New York: Commonwealth Fund, 1936); Roderick Heffron, *Pneumonia: With Special Reference to Pneumococcus Lobar Pneumonia* (New York: Commonwealth Fund, 1939).

9. Regarding the clamoring for sulfapyridine by general practitioners throughout the 1938–39 pneumonia season, see R. W. Weilerstein and John T. Cain, "Memorandum of Interview with Edward A. Lawrence," 1/30/39; R. W. Weilerstein, "Memorandum of Telephone Interview with Dr. John B. Ahouse," 1/31/39 [both in NDA, Vol. II]; Congressman Frank W. Boylan (Alabama) to W. G. Campbell, 2/13/39 [NDA, Vol. III].

10. William Spring to Maxwell Finland, 12/19/39 [Series II, Subseries A, Box 5, Folder 10, MFP]. A month later, Spring would write: "I trust you survived the holidays all right and are now steaming along at full tilt—or do all pneumonias get well at home now with the 'magic medicine.' I hear that Macleod, et al. can't get any more of those young, early, uncomplicated cases to play with" (Spring to Finland, 1/18/40 [Series II, Subseries A, Box 5, Folder 10, MFP]).

11. See, e.g., J. O. Manier, "Sulfanilamide and its Compounds: Their Uses in Medicine," *Journal of the Tennessee Medical Association* 33 (1940): 299.

12. See "Sulfapyridine," *Journal of the American Medical Association* 112 (1939): 1830; Raymond O. Muether, "Modern Trends in Pneumonia Therapy," *Journal of the Missouri State Medical Association* 36 (1939): 471. For the persistence of such concerns a year later, see Francis G. Blake, "The Treatment of Pneumococcal Pneumonia," *New England Journal of Medicine* 223 (1940): 662.

13. Robert A. Kilduffe, "Recent Advances in the Study of Pneumonia," *Journal of the Medical Society of New Jersey* 36 (1939): 648. Italics in the original. As an example of the persisting accumulation of mere "statistics," two Cleveland physicians would offer in early 1940: "In view of the many conflicting results being reported in the treatment of the pneumonias, it was thought that additional statistics would be of use in evaluating present trends in therapy. With sufficient cases listed, one may soon evaluate the relative merits of antipneumococcic sera, sulfapyridine, or a combination of both." No controls were utilized. In Robert A. Reading and Clark H. Millikan, "Experiences in the Treatment of Pneumonia," *Ohio State Medical Journal* 37 (1941): 28.

14. Kilduffe, "Recent Advances," 648. Regarding "sum total," see Maxwell Finland, "Controlling Clinical Therapeutic Experiments with Specific Serums: With Particular Reference to Antipneumococcus Serums," *New England Journal of Medicine* 225 (1941): 496.

15. Jesse G. M. Bullowa, Norman Plummer, and Maxwell Finland, "Sulfapyridine in the Treatment of Pneumonia," *Journal of the American Medical Association* 112 (1939): 570. Their letter likewise alluded to another published two weeks earlier in *JAMA* regarding sulfapyridine by Johns Hopkins' E. Kennerly Marshall, and essentially transposed to the clinical realm Marshall's castigation of investigators for their own flimsy studies and use of sulfapyridine to further their own narrow interests at the expense of larger goals: "In spite of the hopeful outlook in the field of bacterial chemotherapy, certain tendencies which have become obvious in the past three years should cause grave concern to serious and thought-

ful students of the subject. . . . A new and promising field is always immediately invaded by workers from other fields. Results must be obtained over night and reputations made (or blasted) in a month. Instead of the time-honored slow and laborious method of reaching conclusions, some short-cut method is adopted without the investigator (we hope so, at least) being aware that the experiment cannot yield an answer to the question at issue. . . . Many of the investigators who have entered this field have made no attempt to evaluate the significance of their figures or to analyze and test their meaning by even an elementary statistical technique. . . . If investigators refuse to recognize the simplest statistical principles, I suggest that the editors of reputable journals refuse to accept the manuscripts of such investigators and inform them in no uncertain terms of the inadequacy of their results" (Marshall, "An Unfortunate Situation in the Field of Bacterial Chemotherapy," *Journal of the American Medical Association* 112 [1939]: 352).

16. See, for example, R. W. Weilerstein and J. T. Cain, "Memorandum of Interview, Dr. Norman Plummer, Dr. Henning," 1/27/39 [NDA, Vol. II].

17. Although the psychologist Donald T. Campbell coined the terms "internal validity" and "external validity" in the 1950s, nearly twenty years would pass before their usage in the medical literature. See Donald T. Campbell, "Factors Relevant to the Validity of Experiments in Social Settings," *Psychological Bulletin* 54 (1957): 297; Donald T. Campbell and Julian C. Stanley, "Experimental and Quasi-Experimental Designs for Research on Teaching," in *Handbook of Research on Teaching*, ed. N. L. Gage (Chicago: Rand McNally, 1963), 175; Lawrence W. Green, "Evaluation and Measurement: Some Dilemmas for Health Education," *American Journal of Public Health* 67 (1977): 156.

18. Norman Plummer, James Liebmann, Saul Solomon, W. H. Kammerer, Mennasch Kalkstein, and Herbert K. Ensworth, "Chemotherapy versus Combined Chemotherapy and Serum in the Treatment of Pneumonia: A Study of 607 Alternated Cases," *Journal of the American Medical Association* 116 (1941): 2366–71.

19. Norman Plummer, "The Treatment of Pneumonia," *Journal of the Indiana State Medical Society* 35 (1942): 611. Indeed, in the week before embarking on the trial, Plummer had noted to FDA officials: "Under present method of treatment, before the advent of the drug there was a 25% average mortality. With the drug it may go down to 12%. When the proper combination of drug and serum treatment has been worked out, it may go down to 7% or less." See also R. W. Weilerstein and John T. Cain, "Memorandum of Interview, Dr. Norman Plummer, Dr. Henning," 1/27/39 [NDA, Vol. II].

20. Norman Plummer, correspondence attached to Maxwell Finland, "Combined Serotherapy and Chemotherapy in Pneumonia [Correspondence]," *New England Journal of Medicine* 225 (1941): 517.

21. Maxwell Finland, "Controlling Clinical Therapeutic Experiments with Specific Serums," 496. Such concerns had influenced Finland's own first studies comparing serum versus sulfonamides versus combination therapy, when he had admitted: "No attempt was made to carry out any strictly controlled alternation, since previous experience has convinced us of the futility of such attempts when therapeutic agents with known lifesaving properties are available" (Maxwell Finland, Francis C. Lowell, and William C. Spring Jr., "Clinical and Laboratory Studies on the Use of Serum and Sulfapyridine in the Treatment of the Pneumococcal Pneumonias," *New England Journal of Medicine* 222 [1940]: 743).

22. Finland, "Controlling Clinical Therapeutic Experiments with Specific Serums," 501.

23. Summarizing Plummer's studies, in a letter included in the same journal volume, he would continue: "It is impossible to carry out large-scale clinical experiments with strictly scientific controls that are not open to criticism. As a single example, if one works out the probability that the difference in the twenty-four-hour deaths in the two groups is a matter of chance, one finds that it is approximately one out of thirty-five times" (Finland, "Combined Serotherapy and Chemotherapy in Pneumonia," 517).

24. Finland, "Controlling Clinical Therapeutic Experiments with Specific Serums," 502.

25. Ibid., 495–96. Finland did not excuse even himself from such wariness, reflecting that "it is only because we have ourselves been so thoroughly disillusioned when reviewing the results of our clinical results, which we thought were clinically controlled, that we became convinced of how difficult it is to carry out such experiments" (Finland, "Combined Serotherapy and Chemotherapy in Pneumonia," 517).

26. See Finland, "Controlling Clinical Therapeutic Experiments with Specific Serums," 503, 504.

27. Marks, *Progress of Experiment,* 139–40.

28. Finland, "Controlling Clinical Therapeutic Experiments with Specific Serums," 502. It is telling that Finland had not entertained the notion of serum's possible nonspecific effects.

29. Ibid., 502. See also Maxwell Finland, "The Serum Treatment of Lobar Pneumonia," *New England Journal of Medicine* 202 (1930): 1246–47.

30. See Bullowa, in D. C. Stahle, "A Clinical Analysis of Fifteen Thousand Cases of Pneumonia: An Evaluation of the Effectiveness of Various Therapeutic Agents," *Journal of the American Medical Association* 118 (1942): 446; Hobart A. Reimann, "Pneumococcal and 'Virus' Pneumonia," *Bulletin of the New York Academy of Medicine* 17 (1941): 190.

31. Maxwell Finland to Roderick Heffron, 3/12/42 [Series II, Subseries A, Box 2, Folder 41, MFP].

32. Finland, "Controlling Clinical Therapeutic Experiments with Specific Serums," 505.

33. In discussing pharmaceutical company efforts to promote their individual sulfonamide compounds, for example, he had previously noted to Wesley Spink: "From the laboratory studies which the various interested pharmaceutical concerns have made, it is obvious that each firm is indicating a superiority for the particular drug in which it is interested. It is really amazing how the same experiment gives different shades of results, depending on what your interest is" (Maxwell Finland to Wesley Spink, 3/1/40 [Series II, Subseries A, Box 5, Folder 8, MFP]).

34. Finland, "Controlling Clinical Therapeutic Experiments with Specific Serums," 505.

35. Ibid.

36. Norman Plummer, "Combined Serotherapy and Chemotherapy in Pneumonia," 518.

37. Ibid., 517.

38. Ibid., 518.

39. Maxwell Finland to Roderick Heffron, 3/12/42 [Series II, Subseries A, Box 2, Folder 41, MFP]. Finland's persisting ethical concerns with the alternate control trial are evident in the final sentence.

40. For statistical disdain, see Osler Peterson to Maxwell Finland, 10/6/43; Maxwell

Finland to Osler Peterson, 10/8/43 [both in Series II, Subseries A, Box 4, Folder 22, MFP]; Maxwell Finland to Elias Strauss, 3/27/45 [Series II, Subseries A, Box 5, Folder 19, MFP]. For statistical nihilism, in particular concerning the evaluation of the treatment of pneumococcal pneumonias caused by "higher types," see Maxwell Finland, "The Present Status of the Higher Types of Antipneumococcus Serums," *Journal of the American Medical Association* 120 (1942): 1294.

41. Robert G. Petersdorf, "Sulfadiazine," *Journal of the American Medical Association* 251 (1984): 1476.

42. Ibid.

43. Ibid.

44. Maxwell Finland, Elias Strauss, and Osler L. Peterson, "Sulfadiazine: Therapeutic Evaluation and Toxic Effects on Four Hundred and Forty-six Patients," *Journal of the American Medical Association* 116 (1941): 2642.

45. Petersdorff, "Sulfadiazine," 1475.

46. Over the ensuing decade, Finland would come to accept the importance of controlled clinical trials, though "controlled" often continued to simultaneously signify for him the care with which the clinical epidemiological outcomes of such studies were correlated with basic laboratory and clinical findings that made deterministic sense. If Rufus Cole had considered the laboratory as necessarily underlying acceptable clinical care, Finland considered the laboratory as necessarily underlying acceptable clinical studies. See Maxwell Finland, "Antimicrobial Treatment for Viral and Related Infections: I. Antibiotic Treatment of Primary Atypical Pneumonia," *New England Journal of Medicine* 247 (1952): 324; Maxwell Finland to John H. Dingle, 1/28/53; John H. Dingle to Maxwell Finland, 2/3/53; Maxwell Finland to John Dingle, 2/16/53 [all in Series II, Subseries A, Box 2, Folder 6, MFP]. By the mid-1950s, ironically, Finland would become one of the most prominent supporters of "controlled" clinical studies in the country, in efforts to instill therapeutic rationalism and counter ever-increasing pharmaceutical marketing efforts with respect to antibiotics; see, e.g., Maxwell Finland, "Antibacterial Agents: Uses and Abuses in Treatment and Prophylaxis," *Rhode Island Medical Journal* 43 (1960): 500.

47. At times such concerns did appear as an attack on the broad generalizability of the findings of the large hospitals of the Northeast to local communities. See Clarence P. Phillips, discussion following Ben F. Wolverton, "The Treatment of Pneumonia," *Journal of the Iowa State Medical Society* 31 (1941): 530. Such an attack, however, was attenuated by the presence of the pneumonia control programs themselves; see ibid., 527.

48. F. T. Billings Jr., and W. Barry Wood Jr., "Studies on Sulfadiazine. III: The Use of Sulfadiazine in the Treatment of Pneumococcal Pneumonia," *Bulletin of the Johns Hopkins Hospital* 69 (1941): 326; Harry F. Dowling, "Problems Arising in the Chemotherapy of Pneumonia and Meningitis," *Medical Annals of the District of Columbia* 10 (1941): 466–67.

49. Jesse G. M. Bullowa, Edwin E. Osgood, Samuel C. Bukantz, and Inez E. Brownlee, "The Effect of Sulfapyridine Alone and with Serum on Pneumococcic Pneumonia and on Pneumococcus-Infected Marrow Cultures," *American Journal of Medical Science* 199 (1940): 365; Jesse G. M. Bullowa, "Rationale of Specific Therapy for the Pneumococcic Pneumonias," *Psychiatry Quarterly* 14 (1940): 568, 569.

50. W. E. Bunney to Benjamin White, 1/24/38 [Box 203, Folder 1901, Series 18.1

(Grants), RAC]. Frisch's studies were considered by Roderick Heffron "the thing of outstanding importance in the whole [Michigan Pneumonia] program," with the study of the chemotherapeutic treatment of pneumonia considered "next in order." See Roderick Heffron to Barbara S. Quin, 4/20/39 [Box 203, Folder 1903, Series 18.1 (Grants), RAC].

51. J. T. Tripp to Barbara S. Quin, 11/30/39 [Box 203, Folder 1905, Series 18.1 (Grants), RAC]. For the use of the term "individualize," see also Arthur W. Frisch and Alvin E. Price, "Sputum Studies in Pneumonia: The Selection of Therapy," *Annals of Internal Medicine* 15 (1941): 987; Arthur W. Frisch, Alvin E. Price, and Gordon B. Myers, "Pneumococcic Pneumonia: The Selection and Control of Serum and Chemotherapy by Sputum Examination," *American Journal of Medical Science* 205 (1943): 771. For its contemporary use by other clinicians, see also Joe Kopecky, "The Aims and Methods of the Texas Pneumonia Control Program," *Texas State Journal of Medicine* 37 (1941): 392.

52. J. T. Tripp to Elliott S. Robinson, 12/1/39 [Box 203, Folder 1905, Series 18.1 (Grants), RAC].

53. Roderick Heffron, "Michigan Department of Health—Pneumonia Study. Comment on Progress Report, and Visit to Project, by Drs. Robinson and Heffron," 6/22–25/40 [Box 203, Folder 1905, Series 18.1 (Grants), RAC].

54. Frisch and Price, "Sputum Studies in Pneumonia," 992.

55. Much as it led to the curtailment of pneumococcal typing in general, the advent of chemotherapy greatly delimited the national impact of Frisch's work. See Roderick Heffron, "Michigan Department of Health Pneumonia Study: Review of Progress for the Past Two Years, Visit to Project, and Comment on Work Proposed for the Coming Year," 4/30/41 [Box 203, Folder 1907, Series 18.1 (Grants), RAC].

56. Samuel Charles Bukantz, Jesse G. M. Bullowa and Paul F. deGara, "Detection of Free Polysaccharide in Blood of Pneumococcic Pneumonia Patients: Prognosis and Therapy," *Proceedings of the Society for Experimental Biology and Medicine* 41 (1939): 254; Jesse G. M. Bullowa, Samuel C. Bukantz, and Paul F. deGara, "The Balance between Capsular Polysaccharide and Antibody in Relation to the Prognosis and Therapy of Pneumococcal Pneumonia," *Annals of Internal Medicine* 14 (1941): 1357.

57. Bullowa, "Rationale of Specific Therapy for the Pneumococcic Pneumonias," 568. See also Jesse G. M. Bullowa, "The Necessity for 'Typing' Pneumonias," *Journal of the Mount Sinai Hospital* 7 (1941): 319. For Bullowa's recommendation of a two-dimensional axis by which to stratify patients in terms of age and duration of disease (rendered in the setting of his aforementioned defense of serotherapy at the AMA in June of 1941), see Bullowa, in Stahle, "Clinical Analysis of Fifteen Thousand Cases of Pneumonia," 446. For a separate contemporary attempt at stratification along a two-dimensional axis of clinical variables and age, see Robert P. McCombs, "A Prognostic Index in Pneumonia," *Journal of the Tennessee State Medical Association* 34 (1941): 443–48.

58. Cole's ethos in this respect would itself be updated at the time by Marion Blankenhorn: "It is my opinion that the future will not bring us a universal remedy, better than all the rest for every case of pneumonia, but that there will be several—perhaps a number—of best remedies for the particular variety of pneumonia at hand. Instead of a specific for all pneumonias, there will be a specific for each of several varieties" (M.A. Blankenhorn, "Pneumonia Cures," *Ohio State Medical Journal* 36 [1940]: 389).

59. "If the physician knows his patient's response to therapy, he may chart the course of the pneumonia which should be short if appropriate remedies are chosen. It may be long and stormy, if the patient comes for treatment late, and with many invaders aboard who have been given confidence by inadequate or delayed counter-attack" (Bullowa, "The Necessity for 'Typing' Pneumonias," 319). For a similar contemporary use of the metaphor of military generalship in the multi-agent attack on the pneumococcus, see W. F. Drummond, "The Outlook for the Future of Pneumococcic Pneumonia," *Tri-State Medical Journal* 12 (1940): 2537.

60. Bullowa, "Rationale of Specific Therapy," 577. See also Jesse G. M. Bullowa, "Pneumonia," *Hygeia* 19 (1941): 11. For parallels to practitioners' resistance to rules of thumb in determining appropriate recipients of anesthesia in the nineteenth century, see Martin Pernick, *A Calculus of Suffering: Pain, Professionalism, and Anesthesia in Nineteenth-Century America* (New York: Columbia University Press, 1985), 142–47.

61. Bullowa, it should be noted, further challenged William Tillett's experimental findings (discussed in chapter 6) concerning the correlation between antibody responses and recovery in sulfapyridine-treated patients. See Jesse G. M. Bullowa, Paul F. deGara, and Samuel C. Bukantz, "Type-Specific Antibodies in the Blood of Patients with Pneumococcic Pneumonia: Detection, Incidence, Prognostic Significance and Relation to Therapies," *Archives of Internal Medicine* 69 (1942): 13.

62. Ibid., 12. By early 1943, two McGill clinicians would still cite the stratification "aids" afforded by Frisch and Bullowa in guiding clinical choice; see J. C. Meakins and Richard D. McKenna, "An Analysis of Pneumonia Deaths Since the Introduction of Sulfonamide Therapy," *Canadian Medical Association Journal* 48 (1943): 104. For Bullowa's unbowed persistence in rendering such recommendations through the very months before his own death, see Nathan H. Shackman and Jesse G. M. Bullowa, "Sulfadiazine Administered Alone and with Antipneumococcus Serum in the Treatment of Pneumococcic Pneumonia," *Archives of Internal Medicine* 72 (1943): 344–45.

63. W. V. Wilkerson, "Pneumonia," *West Virginia Medical Journal* 38 (1942): 333.

64. Regarding the perceived rapidity of change faced by clinicians at the time, see H. Corwin Hinshaw, "Recent Advances in the Management of the Pneumonias," *Medical Clinics of North America* 23 (1939): 945; Kilduffe, "Recent Advances in the Study of Pneumonia," 646; Roy E. Thomas, "Evaluation of the Newer Therapy in the Pneumonias," *California and Western Medicine* 54 (1941): 106.

65. In this respect, they would set a foundation for still greater efforts in subsequent decades to fill such a "void," as recently described by Jerry Avorn (independently using the same metaphor); see his *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs* (New York: Alfred A. Knopf, 2004), 269–91.

66. By no means were they alone in such efforts, however. Sharp and Dohme (which had acquired the H. K. Mulford company in 1929 and which would merge with Merck in 1953), for example, would report to its sales force with respect to Maxwell Finland's emerging public enthusiasm for sulfapyridine by August of 1939: "Since the pneumonia season is approaching, the above information is of great importance and can be used to advantage in your creative sales activities" (*Sharp and Dohme Extract* 11 [October 1939]: 4). See also "Sulfapyridine in Pneumonia," *New York State Journal of Medicine* 39 (1939): 1512.

67. *The Clinical Use of Sulfapyridine in Pneumococcic Pneumonia* (Rahway, N.J.: Merck and Company, 1939), 3.

68. Ibid., 6–14.

69. Ibid., 19–22.

70. Ibid., 11.

71. Ibid., 37. Later, they would note that "it cannot be definitely stated until further extensive surveys have been made whether the combination of sulfapyridine and specific antiserum will give the best results from a statistical point of view" (ibid.).

72. See John Lesch's forthcoming manuscript on the history of the sulfa drugs. See also "Merck Institute of Therapeutic Research, Sixth Annual Report (1938)"; "Merck Institute of Therapeutic Research, Seventh Annual Report (1939)" [both in ANRP, Box 20, FF 39].

73. See John T. Cain, "Memorandum of Interview with Dr. W. G. Malcom (Medical Director, Lederle), Dr. Clark (Assistant Medical Director, Lederle)," 1/31/39 [NDA, Vol. II].

74. Wilbur Malcolm, Lederle's medical director, had apparently enhanced his own standing within the company through his early positioning of Lederle to embark upon sulfa drug research. See ibid.; Sikharam Prasannna Kumara Gupta and Edgar L. Milford, *In Quest of Panacea: Successes and Failures of Yellapragada Subarow* (Nanuet, N.Y.: Evelyn Publishers, 1987), 111.

75. Tom Mahoney, *The Merchants of Life: An Account of the American Pharmaceutical Industry* (New York: Harper and Brothers, Publishers, 1959), 171. Its sulfadiazine sales alone, for 1943, reached $16 million; see "Statement of W. G. Malcolm," United States Congress, Senate Committee on the Judiciary, Subcommittee on Antitrust and Monopoly, *Administered Prices, Part 24: Administered Prices in the Drug Industry (Antibiotics)*, 86th Congress, 2nd session, 1960, 13635.

76. See John T. Cain, "Memorandum of Interview with Dr. W. G. Malcom (Medical Director, Lederle), Dr. Clark (Assistant Medical Director, Lederle)," 1/31/39 [NDA, Vol. II].

77. Regarding Bullowa, see Benjamin W. Carey to Harry Dowling, 11/18/43 [HDP, Box 2, "Correspondence"]; regarding Finland, see W. G. Malcolm to G. R. Minot, 5/31/39 [Series II, Subseries A, Box 3, Folder 55, MFP].

78. "The Role of Serotherapy in the Treatment of the Pneumonias," *Bulletin of Lederle Laboratories* 7 (February 1939): 3.

79. Ibid., 6, 10. In contrast, they would note that the use of antiserum possessed, "when properly applied, ample statistical support" (10).

80. "Sulfapyridine in the Treatment of Pneumonia," *Bulletin of Lederle Laboratories* 7 (April 1939): 35. Indeed, they now noted that "since May, 1938, a series of articles has appeared in the medical literature, presenting conclusive evidence of the value of sulfapyridine" (39). Cf. the disdain for the initial British studies as voiced in "The Role of Serotherapy in the Treatment of the Pneumonias," 4. For Lederle's release of sulfapyridine, see *American Professional Pharmacist* 5 (1939): 152.

81. "Treatment of Pneumococcal Pneumonias with Sulfapyridine and Type-Specific Antiserums," *Bulletin of Lederle Laboratories* 7 (October 1939): 75; "Sulfapyridine" advertisement on page 77.

82. See also "Sulfapyridine and Type-Specific Serum," advertisement in *Bulletin of Le-*

derle Laboratories 8 (January 1940): 2; "The Treatment of Pneumococcal Pneumonias," *Bulletin of Lederle Laboratories* 8 (October 1940): 66–67.

83. "Pneumonia Drops to 5th Place," advertisement in *Bulletin of Lederle Laboratories* 9 (January 1941): 16.

84. "The Present Status of Pneumonia-Therapy," *Bulletin of Lederle Laboratories* 9 (November 1941): 68, 74. For the persistence of Lederle's own serotherapy-generous indications for up-front combination therapy, see p. 72.

85. By 1941, Lederle's annual sulfadiazine sales (I have been unable to locate sulfapyridine sales reports) exceeded one million dollars, in contrast to approximately $300,000 worth of antipneumococcal antiserum; by 1942, the figures were over nine million dollars, and just under $400,000, respectively. See "Statement of W. G. Malcolm," United States Congress, 13635.

86. Regarding such pharmaceutical and marketing revolutions, respectively, see Milton Silverman and Philip Lee, *Pills, Profits, and Politics* (Berkeley and Los Angeles: University of California Press, 1974), 1–23; Jeremy A. Greene, "The Therapeutic Transition: Pharmaceuticals and the Marketing of Chronic Disease" (Ph.D. diss., Harvard University, 2005).

Chapter 8. The Dismantling of Pneumonia as a Public Health Concern

1. Again, for the term "therapeutic rationalism," see James C. Whorton, "'Antibiotic Abandon': The Resurgence of Therapeutic Rationalism," in *The History of Antibiotics: A Symposium,* ed. John Parascandola (Madison, Wis.: American Institute of the History of Pharmacy, 1980), 125–36. For the notion of a "republic of science" to which clinicians voluntarily subscribe, see Harry Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (New York: Cambridge University Press, 1997), 4–5, 231–38.

2. Regarding the depletion of the physician force broadly, see Jonathan Engel, *Doctors and Reformers: Discussion and Debate over Health Policy, 1925–1950* (Columbia: University of South Carolina Press, 2002), 190–91. Regarding the depletion of the public health apparatus, see Thomas Parran, "Wartime Problems of the Public Health Service" (Annual Congress on Medical Education and Licensure, American Medical Association, 2/16/42), [TPP, Box 43, FF 597]; W. C. Williams to Harry C. Handley, 5/11/42; W. C. Williams to Clarence Scamman, 6/4/42 [both in Box 36, Folder 521, Series 12.2, RAC]; Thomas Dublin to Maxwell Finland, 8/17/42 [Series II, Subseries A, Box 2, Folder 12, MFP]; C. C. Young to Barbara S. Quin, 12/23/42 [Box 203, Folder 1908, Series 18.1 (Grants), RAC].

3. Engel, *Doctors and Reformers,* 191–95.

4. Elizabeth Fee, "The Origins and Development of Public Health in the United States," in *Oxford Textbook of Public Health,* 3rd ed., Volume I: *The Scope of Public Health* (New York: Oxford University Press, 1997), 46–47.

5. Edward L. Bortz, "Therapeutics of Pneumonia on a Statewide Basis," *Journal of the American Medical Association* 121 (1943): 107. For the stated necessity of the cooperation between public health representatives and private practitioners in controlling pneumonia, see Bortz and Hobart Reimann, in ibid., 112, 113.

6. Thomas Parran, "Radio Broadcast" (Instructive Visiting Nurse Society, 4/20/40), [TPP, Box 41, FF 548].

7. Thomas Parran, "Health is on the March" (Office of War Information Radio Transcription, 1/28/44), [TPP, Box 45, FF 645]; Parran, "The Expanding Field of Public Health and Preventive Medicine" (Annual Congress on Medical Education and Licensure, American Medical Association, 2/14/44), [TPP, Box 45, FF 648]; Parran, "State of the Nation's Health" (State and Territorial Health Officers Conference, 3/21/44), [TPP, Box 45, FF 652]; Parran, "The Health of the Nation" (Hearings before Subcommittee on Appropriation, 3/28/44), [TPP, Box 45, FF 653]. For the transformation of Sumner County's (Tenn.) own Pneumonia-Tuberculosis Control Program into a Tuberculosis Control Program only, see R. H. Hutcheson to Clarence Scamman, 3/25/44; E. P. Bowerman, "Remarks Concerning the Tuberculosis Program in Sumner County," 3/27/44 [both in Box 36, Folder 522, Series 12.2, RAC].

8. Thomas Parran, "New Frontiers in Medicine" (Commencement Exercises, University of Utah, 9/10/44), [TPP, Box 46, FF 681].

9. Parran, "The Expanding Field of Public Health and Preventive Medicine." Compare such a marginalization of pneumonia as a research entity, on the eve of the expansion of the NIH, with pneumonia's prominence as such an entity four decades earlier, on the eve of the opening of the Hospital of the Rockefeller Institute.

10. From 1941 to 1945, federal support of the state pneumonia control programs declined from $523,225 to $40,802. No funding was provided beyond 1945. See *Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1941* (Washington, D.C.: U.S. Government Printing Office, 1941), 14; *Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1945* (Washington, D.C.: U.S. Government Printing Office, 1945), 153.

11. W. W. G. Maclachlan, in Bernard J. McCloskey, "Five Years of Pneumonia Control in Cambria County, Pennsylvania," *Pennsylvania Medical Journal* 46 (1943): 483. Regarding Maclachlan, long an advocate of quinine derivatives in the treatment of pneumonia, see E. Bayley Buchanan, *William Watt Graham Maclachlan, M.D.: Pittsburgh's Pneumonia Doctor* (privately published, 1997).

12. Joseph H. Pratt, Isadore Olef, and Joseph Rosenthal, "Team Work in the Present-Day Treatment of Pneumonia," *Bulletin of the New England Medical Center* 3 (1941): 9–12. With foresight, they asked, regarding sulfa treatment: "Will the busy practicing doctor expend the time required to make the necessary tests [of sulfa levels and renal and hematologic function]? In fact, how can he find the time if he has other urgent calls on the day he discovers he has on his hands a case of pneumonia?" (10).

13. David D. Rutstein to W. G. Campbell, 2/7/39 [NDA, Vol. III]. For early confirmation of such fears, see James Clement Hart, "The Program for Control of Pneumonia in New Haven," Master of Public Health thesis, Yale University School of Medicine, 1939, 50, 82 [YU, Y12PM15].

14. Only 4,349 out of 9,295 cases were typed for the 1940–41 season (Bortz, "Therapeutics of Pneumonia on a Statewide Basis," 109). Similarly, regarding the lack of typing performed in Tennessee under the purview of the Commonwealth Fund, see Barry C. Smith, "Memorandum to Miss Rudolph," 4/6/42 [Box 36, Folder 521, Series 12.2, RAC].

15. Horace P. Marvin, Franklin D. Owings, and Edward K. Edelson, "Pneumonia Therapy with Sulfathiazole in Military Practice," *Military Surgeon* 91 (1942): 57.

16. Maine C. Andersen, "In View of Present Day Treatment, Are Typing and Serums Necessary?" *Journal of the Omaha Mid-West Clinical Society* 5 (1944): 48.

17. Such sentiments had already begun upon sulfapyridine's general release for sale. Harvard's Charles F. McKhann, who in January of 1939 had been one of the more cautious respondents to the first wave of FDA inquiry regarding sulfapyridine's release, had by the end of March of that year been widely cited as stating that "people just won't die from pneumonia any more." See "Killer Killed," *Time,* 27 March 1939, 28; cf. McKhann to W. G. Campbell, 1/7/39 [NDA, Vol. II].

18. Russell L. Cecil, in Edward L. Bortz, "Pneumonia in Pennsylvania," *Transactions of the American Clinical and Climatological Association* 56 (1940): 120. For his private considerations to this effect as early as from January of 1939, see Theodore G. Klumpp and R. W. Weilerstein, "Memorandum of Interview with Dr. Russell Cecil," 1/31/39 [NDA, Vol. II].

19. The steady twentieth-century march of military imagery to describe the "attack" on the diplococcus—at both the individual and society levels—accelerated dramatically in the peri–World War II era. Regarding the individual practitioner, Merck's advertising for its sulfa drugs most dramatically drew attention from 1941 to 1945 to the "weapons" placed in the hand of the physician; see, e.g., "Serving on all Fronts," "Arsenal of 'Merciful Munitions'" [both in MA, "Advertisements, 1941–42"]. Regarding society's "attack" on pneumonia, see, e.g., "Nine Battle Lines Marked in Anti-Pneumonia War Plan," *Science News Letter* 36 (1939): 254.

20. Edward Lee Copley, "Pneumonia in Virginia: A Series of Fifty-Three Cases," *Southern Medicine and Surgery* 104 (1942): 142. Proclaimed a Tennessee practitioner the same year: "If the patient with lobar pneumonia entering a hospital tonight were in a condition and knew enough of the facts to reflect on his prospects for a speedy recovery, he would be all smiles. . . . In the near future we may expect to see even an apathy on the part of his kin when they are told that he has only pneumonia" (Charles P. Wofford, "Present-Day Management of Pneumonia," *Journal of the Tennessee State Medical Association* 35 [1942]: 123). See also, "Only Pneumonia," *Science News Letter* 48 (1945): 380; "Pneumonia," *Life Magazine,* 13 February 1950, 53.

21. Andersen, "In View of Present Day Treatment, Are Typing and Serums Necessary?" 48.

22. Norman Plummer, "The Treatment of Lobar Pneumonia" *Bulletin of the New York Academy of Medicine* 20 (1944): 73. The most famously uttered reformulation of pneumonia at this time came from Winston Churchill, who upon being cured of pneumonia via "M&B," remarked that "there is no doubt that pneumonia is a very different illness from what it was before this marvelous drug was discovered." Widely reported in Great Britain, his statement appeared in this country in "Admirable M&B," *Time,* 10 January 1944, 75. See also John E. Lesch, "The Discovery of M&B 693 (Sulfapyridine)," in *The Inside Story of Medicines: A Symposium,* ed. Gregory J. Higby and Elaine C. Stroud (Madison, Wis.: American Institute of the History of Pharmacy, 1997), 102.

23. H. J. Shaughnessy, in Howard A. Lindberg, "The Illinois Pneumonia Control Pro-

gram," *Illinois Medical Journal* 76 (1939): 89; W. F. Drummond, in C. P. Herrington, "Chemotherapy in Pneumonia," *New Orleans Medical and Surgical Journal* 93 (1941): 353; Jesse G. M. Bullowa, "The Necessity for 'Typing' Pneumonias," *Journal of the Mount Sinai Hospital* 7 (1941): 321; A. M. Wolfe, "Colorado Pneumonia Experience, 1939 and 1940," *Rocky Mountain Medical Journal* 39 (1942): 200; Roderick Heffron to Barry Smith, 4/7/42 [Box 36, Folder 521, Series 12.2, RAC].

24. "The Diagnosis and Treatment of Pneumonia: Recommendations by the Pneumonia Advisory Committee of the New York City Department of Health," *New York State Journal of Medicine* 44 (1944): 409. See also Maxwell Finland to John W. Brown, 2/4/44 [Series II, Subseries A, Box 1, Folder 48, MFP].

25. "The Diagnosis and Treatment of Pneumonia: Recommendations by the Pneumonia Advisory Committee of the New York City Department of Health," 409. See also James F. Waddill, "Clinical Management of Lobar Pneumonia," *Virginia Medical Monthly* 71 (1944): 14.

26. William B. McIlwaine, "The Use of Sulfapyridine and Sulfathiazole in General Practice," *Virginia Medical Monthly* 68 (1941): 410–11. As McIlwaine remarked of physiological support: "Our anti-aircraft barrage of rest, air and symptomatic treatment failed so often! While they served well at times, they were no match for an enemy of such strength and ferocity" (410).

27. Plummer, "Treatment of Lobar Pneumonia," 83.

28. Directly contradicting Cole's ideology of specificity, for example, Lederle reported that the Aureomycin (chlortetracycline) treatment of atypical (considered, at the time, "virus") pneumonia "indicated the practicability of using a specific chemotherapeutic agent against an infection of unknown etiology" ("Why is Aureomycin the Broad-Spectrum Antibiotic of Choice in the United States and Throughout the World for Pneumonia?" *Aureomycin Digest* 2 [October 1952], cover page).

29. H. C. Hinshaw, "Chemotherapy in Pneumonia," *Proceedings of the Staff Meetings of the Mayo Clinic* 14 (1939): 771. He continued: "For these reasons, I much prefer the less toxic and more dependable drugs such as neoprontosil or sulfanilamide for respiratory infections other than pneumonia, if any chemotherapy at all for such cases is justifiable."

30. Wendell J. Stainsby, "Pneumonia in General Practice," *Pennsylvania Medical Journal* 47 (1943): 562; O. H. Robertson, "Newer Knowledge Concerning the Inception of Pneumonia and its Bearing on Prevention," *Annals of Internal Medicine* 18 (1943): 12.

31. Drummond, in Herrington, "Chemotherapy in Pneumonia," 353; Morton Hamburger Jr., L. H. Schmidt, Clara L. Sesler, J. M. Ruegsegger, and Eda S. Grupen, "The Occurrence of Sulfonamide-Resistant Pneumococci in Clinical Practice," *Journal of Infectious Diseases* 73 (1943): 12–30; Richard A. Kern, "Abuse of Sulfonamides in the Treatment of Acute Catarrhal Fever," *United States Naval Academy Bulletin* 44 (1945): 686. Cecil and Plummer, however, did advocate for such prophylaxis among those patients whose upper respiratory tract infections were almost uniformly followed by more severe infections; see Russell L. Cecil, Norman Plummer, and Wilson G. Smillie, "Sulfadiazine in the Treatment of the Common Cold," *Journal of the American Medical Association* 124 (1944): 14.

32. Whorton, "'Antibiotic Abandon,'" 129–31.

33. The Kefauver hearings were initially inspired chiefly on account of pharmaceutical

pricing concerns in the wake of the post–World War II pharmaceutical "revolution," before expanding into a general indictment of the pharmaceutical industry at large. A stimulus to such expansion concerned the scandalous realization that Henry Welch, the FDA's director of the Division of Antibiotics, received personal compensation from pharmaceutical companies for advertising within—and reprints derived from—academic journals he edited. The degree to which tension between Finland and Dowling, on the one hand, and Welch on the other, concerning the rational application of antibiotics (especially the use of "fixed-dose combination" antimicrobials opposed by Finland and Dowling and espoused by Welch and the pharmaceutical industry) spilled over into Welch's own undoing warrants further detailed examination. Regarding such antibiotic concerns, see John Lear, "Taking the Miracle Out of the Miracle Drugs," *Saturday Review,* 23 January 1959, 41; John Lear, "The Certification of Antibiotics," *Saturday Review,* 7 February 1959, 47. Regarding the general events leading to the Kefauver hearings (and the later passage of the Kefauver-Harris amendments in the wake of the thalidomide tragedy), see Richard Harris, *The Real Voice* (New York: Macmillan, 1964); Harry F. Dowling, *Medicines for Man: The Development, Regulation, and Use of Prescription Drugs* (New York: Alfred A. Knopf, 1970), 196–202; Philip J. Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (New York: Alfred A. Knopf, 2003), 129–65.

34. Maxwell Finland to Louis S. Goodman, 6/1/61 [HDP, Box 2, "Correspondence," filed with "Goodman"].

35. Dowling, *Medicines for Man,* 162–64, 170–77.

36. C. Joseph Stetler to Harry Dowling, 6/16/61 [HDP, Box 2, "Correspondence"]. Dowling penciled in a question mark next to the statement that "it works out well." For contemporary disagreement with AMA policy, see Louis S. Goodman to Maxwell Finland, 6/7/61; Finland to Goodman, 6/12/61; Louis S. Goodman to Harry Dowling, 6/20/61 [all in HDP, Box 2, "Correspondence"]; "Ethical Drugs—Who Shall Educate the Physician?" *New England Journal of Medicine* 265 (1961): 910–11.

37. Edward D. Kilbourne to George P. Larrick, 10/30/63 [HDP, Box 2, "Correspondence," filed with "Larrick"].

38. Such a withdrawal was implemented in the wake of the Drug Efficacy Studies of the late 1960s, which, on the basis of the Kefauver-Harris Amendments, empowered the FDA, assisted by the National Academy of Sciences and the National Research Council, to evaluate all drugs introduced in America between 1938 and 1962. Regarding the Drug Efficacy Studies broadly, see Milton Silverman and Philip Lee, *Pills, Profits, and Politics* (Berkeley and Los Angeles: University of California Press, 1974), 121–34. Regarding the explosive case of the fixed combination antimicrobial Panalba in particular, see also Morton Mintz, "FDA and Panalba: A Conflict of Commercial, Therapeutic Goals?" *Science* 165 (1969): 875–81.

39. For example, Norris Brookens (the former first president of the Illinois Society of Internal Medicine) wrote to Dowling by late 1963: "I have been disturbed because the detail men are apparently putting on a full-time effort to persuade physicians to use staphicillin for every putative Staphylococcal infection. Should not this drug be reserved? It seems to me that the rights of patients have some precedence over the rights of stockholders." Dowling could only reply: "I suppose we come back to the conclusion that we can only do

so much (and only should do so much) by law and that most of our reforms must come by changing the attitudes of the profession." See Norris Brookens to Harry Dowling, 9/16/63; Harry Dowling to Norris Brookens, 9/25/63; see also William S. Jordan to Harry Dowling, 9/23/63 [all in HDP, Box 2, "Correspondence"].

Still, Dowling and his colleagues realized that, as Cole had faced over four decades earlier, they faced strong adversaries in the men of commerce. Wrote the medical director of Lederle to Dowling, in the setting of Dowling's opposition to combination antimicrobial/antihistamines: "We feel that patients with underlying chronic pulmonary disease, . . . *as well as ambulatory patients who must remain active in their vocations,* justifies the availability of this product for the prevention and treatment of upper respiratory bacterial infections and for concomitant symptomatic relief [italics added]" (B. W. Carey to Harry Dowling, 9/6/63 [HDP, Box 2, "Correspondence"].

40. William A. Nolen and Donald E. Dille, "Use and Abuse of Antibiotics in a Small Community," *New England Journal of Medicine* 257 (1957): 33–34.

41. Ernest Jawetz, "Patient, Doctor, Drug, and Bug," *Antibiotics Annual* (1957–58): 295.

42. See Whorton, "'Antibiotic Abandon,'" 129–30; Maxwell Finland, "Clinical Uses of the Presently Available Antibiotics," *Antibiotics Annual* (1953–1954): 25; Hobart A. Reimann, "The Misuse of Antimicrobics," *Medical Clinics of North America* 45 (1961): 849.

43. Henry E. Simmons and Paul D. Stolley, "This Is Medical Progress? Trends and Consequences of Antibiotic Use in the United States," *Journal of the American Medical Association* 227 (1974): 1023–28.

44. Maxwell Finland, "Increased Resistance in the Pneumococcus," *New England Journal of Medicine* 284 (1971): 212. In 1957 Edward Curnen had written to Finland regarding a possible penicillin-resistant pneumococcal strain from a military source. Finland, while happily agreeing to "help out in any way" with such an investigation, nevertheless replied at the time that "I have had no encounter with any such cases and I rather doubt that they really exist." It is unclear what became of the strain, but it does not appear to have been sent to Finland. See Edward C. Curnen to Maxwell Finland, 3/19/57; Maxwell Finland to Edward C. Curnen, 4/1/57 [both in Series II, Subseries A, Box 2, Folder 1, MFP]; see also Elmer M. Purcell to Maxwell Finland, 2/16/54; Maxwell Finland to Elmer M. Purcell, 2/24/54 [both in Series II, Subseries A, Box 4, Folder 36, MFP].

45. Finland, "Increased Resistance in the Pneumococcus," 213. The first officially designated penicillin-resistant pneumococcal strain had been identified in Australia in 1967, with the New Guinea investigation conducted as a follow-up study of the potential benefits of "penicillin prophylaxis." See D. Hansman and M. M. Bullen, "A Resistant Pneumococcus," *Lancet* 2 (1967): 264–65; David Hansman, Heatherbell Glasgow, John Sturt, Lorraine Devitt, and Robert Douglas, "Increased Resistance to Penicillin of Pneumococci Isolated from Man," *New England Journal of Medicine* 284 (1971): 175–77.

46. Maxwell Finland, "And the Walls Came Tumbling Down: More Antibiotic Resistance, and Now the Pneumococcus," *New England Journal of Medicine* 299 (1974): 771; Gene H. Stollerman, "Trends in Bacterial Virulence and Antibiotic Susceptibility: Streptococci, Pneumococci, and Gonococci," *Annals of Internal Medicine* 89 (1978): 747; Alfred J. Saah, Joseph P. Mallonee et al., "Relative Resistance to Penicillin in the Pneumococcus," *Journal of the American Medical Association* 243 (1980): 1827. The first penicillin-resistant pneu-

mococcus identified in North America had been reported in 1974; see J. M. S. Dixon, "Pneumococcus with Increased Resistance to Penicillin," *Lancet* 2 (1974): 474.

47. Joel Ward, "Antibiotic-Resistant *Streptococcus pneumoniae:* Clinical and Epidemiologic Aspects," *Reviews of Infectious Diseases* 3 (1981): 263.

48. John S. Spika, Richard R. Facklam, Brian D. Plikaytis, and Margaret J. Oxtoby, "Antimicrobial Resistance of *Streptococcus pneumoniae* in the United States, 1979–1987," *Journal of Infectious Diseases* 163 (1991): 1277.

49. An ISI Essential Science Indicators search, conducted in 2003, of the "most-cited papers on antibiotic resistance in the past decade," found three of the top four papers cited to concern pneumococcal resistance. Assessed at *www.esi-topics.com/anti-res/papers/a1.html* (February 2003).

50. Harold C. Neu, "The Crisis in Antibiotic Resistance," *Science* 257 (1992): 1064; Mitchell L. Cohen, "Epidemiology of Drug Resistance: Implications for a Post-Antimicrobial Era," *Science* 257 (1992): 1050. See also Calvin M. Kunin, "Resistance to Antimicrobial Drugs: A Worldwide Calamity," *Annals of Internal Medicine* 118 (1993): 557.

51. Robert F. Breiman, Jay C. Butler, Fred C. Tenover, John A. Elliott, and Richard R. Facklam, "Emergence of Drug-Resistant Pneumococcal Infections in the United States," *Journal of the American Medical Association* 271 (1994): 1835; Daniel B. Jernigan, Martin S. Cetron, and Robert F. Breiman, "Minimizing the Impact of Drug-Resistant *Streptococcus pneumoniae* (DRSP): A Strategy from the DRSP Working Group," *Journal of the American Medical Association* 275 (1996): 206–9.

52. Benjamin Schwartz, David M. Bell, and James M. Hughes, "Preventing the Emergence of Antimicrobial Resistance: A Call for Action by Clinicians, Public Health Officials, and Patients," *Journal of the American Medical Association* 278 (1997): 945; Neu, "The Crisis in Antibiotic Resistance," 1072.

53. Michael S. Simberkoff, "Drug-Resistant Pneumococcal Infections in the United States: A Problem for Clinicians, Laboratories, and Public Health," *Journal of the American Medical Association* 271 (1994): 1875; Joseph F. Plouffe, Robert F. Breiman, and Richard R. Facklam, "Bacteremia with *Streptococcus pneumoniae:* Implications for Therapy and Prevention," *Journal of the American Medical Association* 275 (1996): 197.

54. Ralph Gonzales, John F. Steiner, and Merle A. Sande, "Antibiotic Prescribing for Adults with Colds, Upper Respiratory Tract Infections, and Bronchitis by Ambulatory Care Physicians," *Journal of the American Medical Association* 278 (1997): 901.

55. Ralph Gonzales, Daniel C. Malone, Judith H. Maselli, and Merle A. Sande, "Excessive Antibiotic Use for Acute Respiratory Infections in the United States," *Clinical Infectious Diseases* 33 (2001): 757. A further study of such national data from 1997–99 would find that 46 percent of patients with the common cold or a nonspecific upper respiratory tract infection would still be given antibiotics. Over half of them were prescribed broad-spectrum agents. In Michael A. Steinman, C. Seth Landefeld, and Ralph Gonzales, "Predictors of Broad-Spectrum Antibiotic Prescribing for Acute Respiratory Tract Infections in Adult Primary Care," *Journal of the American Medical Association* 289 (2003): 719. See also Michael A. Steinman, Ralph Gonzales, Jeffrey A. Linder, and C. Seth Landfield, "Changing Use of Antibiotics in Community-Based Outpatient Practice," *Annals of Internal Medicine* 138 (2003): 525–33.

56. Cynthia G. Whitney, Monica M. Farley et al., "Increasing Prevalence of Multidrug-

Resistant *Streptococcus pneumoniae* in the United States," *New England Journal of Medicine* 343 (2000): 1917–18. "Invasive" disease "was defined by the isolation of *S. pneumoniae* from a normally sterile body site."

57. See, e.g., Jernigan, Cetron, and Breiman, "Minimizing the Impact of Drug-Resistant Streptococcus pneumoniae (DRSP)," 206–9.

58. For the use of the term "emergency," see Cohen, "Epidemiology of Drug Resistance," 1054.

59. Peter English, "Therapeutic Strategies to Combat Pneumococcal Disease: Repeated Failure of Physicians to Adopt Pneumococcal Vaccine, 1900–1945," *Perspectives in Biology and Medicine* 30 (1987): 170–85.

60. Rufus Cole to Roger Morris, 10/31/17 [RCP]. See also Almroth E. Wright, W. Parry Morgan, L. Colebrook, and R. W. Dodgson, "Observations on Prophylactic Inoculation against Pneumococcus Infections, and on the Results which have been Achieved by It," *Lancet* 1 (1914): 87–95; F. S. Lister, "Prophylactic Inoculation of Man against Pneumococcal Infections, and More Particularly against Lobar Pneumonia; Including a Report upon the Results of the Experimental Inoculation, with a Specific Group Vaccine, of the Native Mine Labourers Employed upon the Premier (Diamond) Mine and the Crown (Gold) Mines in the Transvaal and the De Beers (Diamond) Mines at Kimberley—Covering the Period from November 1, 1916 to October 31, 1917," *Publications of the South African Institute for Medical Research* 1 (1917): 303–32.

61. Russell L. Cecil and J. Harold Austin, "Results of Prophylactic Inoculation against the Pneumococcus in 12,519 Men," *Journal of Experimental Medicine* 28 (1918): 19–41; Russell L. Cecil and Henry F. Vaughn, "Results of Prophylactic Vaccination against Pneumonia at Camp Wheeler," *Journal of Experimental Medicine* 29 (1919): 457–83. For a discussion of the two studies and for the use of the term "confounding," see English, "Therapeutic Strategies to Combat Pneumococcal Disease," 177–78.

62. For Cole's initial enthusiasm for the studies, see Rufus Cole to S. G. Rosenbaum, 11/19/18 [RCP]. For his more measured approach at the studies' completion, see Rufus Cole, "Acute Lobar Pneumonia—Survey of Literature from January 1, 1925–July 1, 1925," in *Nelson's Loose-Leaf Living Medicine* (New York: Thomas Nelson and Sons, 1925), 419–20. For his continued waning of enthusiasm, see Cole, "The Outlook for Overcoming Pneumonia—Stenographic Notes of Talk at Meeting of the New York State Association of Public Health Laboratories in November 1933" [RCP, filed under "New York State Department of Health #5"]; Rufus Cole, "The Outlook for Overcoming Pneumonia," *Canadian Medical Association Journal* 30 (1934): 239.

63. Thomas Parran, "Pneumonia Conference: Opening Statement," 11/12/37 [RG443 0425, Box 14].

64. See Roderick Heffron to Louis Dublin, 7/20/37; Lloyd D. Felton to Louis Dublin, 7/20/37 [both in LDP, Box 16, "Pneumonia"].

65. Thomas Francis Jr., and William S. Tillett, "Cutaneous Reactions in Pneumonia: The Development of Antibodies Following the Intradermal Injection of Type-Specific Polysaccharide," *Journal of Experimental Medicine* 52 (1930): 573–85.

66. G. M. Ekwurzel, J. S. Simmons, Louis I. Dublin, and Lloyd D. Felton, "Studies in Immunizing Substances in Pneumococci. VII: Report on Field Tests to Determine the Pro-

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72. William W. Bolton, "Pneumonia's Waterloo?" *Hygeia* 25 (1947): 50.

73. Walsh McDermott, in "Conference on Therapy: Treatment of Pneumonia," *American Journal of Medicine* 4 (1948): 431; Harry F. Dowling and Mark H. Lepper, "The Effect of Antibiotics (Penicillin, Aureomycin, and Terramycin) on the Fatality Rate and Incidence of Complications in Pneumococcic Pneumonia: A Comparison with Other Methods of Therapy," *American Journal of Medical Science* 222 (1951): 398, 402; Wesley Spink to Maxwell Finland, 1/2/53 [Series II, Subseries A, Box 5, Folder 8, MFP].

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77. Ibid., 763, 769. Among those who received antibiotics, the mortality rate was 17 percent.

78. Ibid., 762, 763. The mortality rate was 13 percent among those below the age of sixty, 49 percent among those sixty and older.

79. Ibid., 773, 774.

80. Ibid., 774–75. Reasoned Austrian: "If it is worthwhile to invest large sums in the palliation and cure of neoplastic and cardiovascular diseases, . . . it seems reasonable to utilize available knowledge to reduce the morbidity and mortality resulting from one of the most common bacterial infections in our society" ("The Current Status of Bacteremic Pneumococcal Pneumonia," 124). In an ironic affirmation, *Newsweek* reported Austrian's findings in a medicine column entitled "Still a Killer," a far cry from their "Pneumonia Licked" column of twelve years earlier. Cf. "Pneumonia Licked," *Newsweek,* 6 August 1951, 50; "Still a Killer," *Newsweek,* 13 May 1963, 91.

81. Regarding the aborted initial effort among the National Institute of Allergy and Infectious Diseases, Eli Lilly and Company, and Austrian, see Louis Galambos and Jane Eliot Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895–1995* (New York: Cambridge University Press, 1995), 160–61.

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83. Regarding Austrian's collaboration with Merck's Maurice Hilleman without federal financial support, see Galambos and Sewell, *Networks of Innovation,* 161–62. Such collaboration is somewhat ironic, given Penn and Merck's collaboration on the dissemination more than three decades previously of the very specific, sulfapyridine, which had led to the dismantling of pneumonia as a public health concern.

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87. Robert Austrian, "Some Observations on the Pneumococcus and on the Current Status of Pneumococcal Disease and its Prevention," *Reviews of Infectious Disease* 3 (1981): S13–S14; Michael S. Simberkoff, Anne P. Cross, Mohamed Al-Ibrahim et al., "Efficacy of Pneumococcal Vaccine in High-Risk Patients: Results of a Veterans Administration Cooperative Study," *New England Journal of Medicine* 315 (1986): 1318–27.

88. Robert Austrian, "A Reassessment of Pneumococcal Vaccine," *New England Journal of Medicine* 310 (1984): 652; Eugene D. Shapiro, "Pneumococcal Vaccine Failure" (Letter), *New England Journal of Medicine* 316 (1987): 1272–73; F. Marc LaForce, "Pneumococcal Vaccine: An Emerging Consensus," *Annals of Internal Medicine* 108 (1988): 757.

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cians," *Chest* 91 (1987): 438; Walter W. Williams, Meredith A. Hickson, Mark A. Kane et al., "Immunization Policies and Vaccine Coverage among Adults: The Risk for Missed Opportunities," *Annals of Internal Medicine* 108 (1988): 619. For the persistence of low coverage throughout the late 1980s, see David S. Fedson, "Pneumococcal Vaccination in the United States and 20 Other Developed Countries, 1981–1996," *Clinical Infectious Diseases* 26 (1998): 1119. Such rates occurred despite the pneumovax's having been the first subject of direct-to-consumer advertising of prescription drugs, starting in October of 1981. See Mickey C. Smith, "Historical Perspectives on the Marketing of Medicines," in *The Inside Story of Medicines,* 270; "Advertisement," *Reader's Digest* 119 (October 1981): 13.

90. For a contemporary general treatise concerning such "limitations," see Alvan R. Feinstein, "An Additional Basic Science for Clinical Medicine: II. The Limitations of Randomized Trials," *Annals of Internal Medicine* 99 (1983): 544–50.

91. Austrian, "A Reassessment of Pneumococcal Vaccine," 652–53.

92. Regarding case control studies—retrospective studies comparing outcome rates among vaccinated patients matched against unvaccinated "controls," yet potentially confounded by unknown further factors rendering the two groups unequal—see John D. Clemens and Eugene D. Shapiro, "Resolving the Pneumococcal Vaccine Controversy: Are There Alternatives to Randomized Clinical Trials?" *Reviews of Infectious Diseases* 6 (1984): 589–600; Eugene D. Shapiro and John D. Clemens, "A Controlled Evaluation of the Protective Efficacy of Pneumococcal Vaccine for Patients at High Risk of Serious Pneumococcal Infections," *Annals of Internal Medicine* 101 (1984): 325–30. Regarding indirect cohort studies—in which the pneumococcal serotypes found among bacteremic vaccinated patients were compared to those found among bacteremic unvaccinated patients—see Claire V. Broome, Richard R. Facklam, and David W. Fraser, "Pneumococcal Disease after Pneumococcal Vaccination: An Alternative Method to Estimate the Efficacy of Pneumococcal Vaccine," *New England Journal of Medicine* 303 (1980): 549–52.

93. Fedson, "Influenza and Pneumococcal Immunization Strategies for Physicians," 437.

94. Robert Austrian, "Pneumococcal Infection," *Preventive Medicine* 3 (1974): 445; Robert Austrian, "Pneumococcal Infection and Pneumococcal Vaccine," *New England Journal of Medicine* 297 (1977): 939; F. Marc Laforce and Theodore C. Eickhoff, "Pneumococcal Vaccine: The Evidence Mounts," *Annals of Internal Medicine* 104 (1986): 110; Claire V. Broome and Robert F. Breiman, "Pneumococcal Vaccine—Past, Present, and Future," *New England Journal of Medicine* 325 (1991): 1507.

95. Fedson, "Pneumococcal Vaccination in the United States and 20 Other Developed Countries," 1119.

96. Robert F. Breiman, "Editorial Response: Prevention of Pneumococcal Disease—A New Romance Begins," *Clinical Infectious Diseases* 26 (1998): 1124. Fedson credited the increase in vaccination to "greater acceptance of retrospective studies showing the clinical effectiveness of vaccination and increased attention to adult immunization by federal agencies and professional organizations," but these appear to have played far less critical roles. In Fedson, "Pneumococcal Vaccination in the United States and 20 Other Developed Countries," 1119.

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see Jan V. Hirschmann and Benjamin A. Lipsky, "The Pneumococcal Vaccine after 15 Years of Use," *Archives of Internal Medicine* 154 (1994): 373–77; Lorna Watson, Brenda J. Wilson, and Norman Waugh, "Pneumococcal Polysaccharide Vaccine: A Systematic Review of Clinical Effectiveness in Adults," *Vaccine* 20 (2002): 2166–73. See, in contrast, David S. Fedson, "The Clinical Effectiveness of Pneumococcal Vaccination: A Brief Report," *Vaccine* 17 (1999): S88. For the most recent indirect cohort study indicating the efficacy of the polysaccharide vaccine in preventing pneumococcal bacteremia (though not pneumococcal pneumonia per se), see Lisa A. Jackson et al., "Effectiveness of Pneumococcal Polysaccharide Vaccine in Older Adults," *New England Journal of Medicine* 348 (2003): 1747–55.

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99. Cynthia G. Whitney, Monica M. Farley, James Hadler et al., "Decline in Invasive Pneumococcal Disease after the Introduction of Protein-Polysaccharide Conjugate Vaccine," *New England Journal of Medicine* 348 (2003): 1737–46.

100. Fedson, "Influenza and Pneumococcal Immunization Strategies for Physicians," 440; Tammy A. Mieczkowski and Stephen A. Wilson, "Adult Pneumococcal Vaccination: A Review of Physician and Patient Barriers," *Vaccine* 20 (2002): 1383, 1386.

101. Regarding clinicians, see Robert H. Pantell and Thomas J. Stewart, "The Pneumococcal Vaccine: Immunization at a Crossroad," *Journal of the American Medical Association* 241 (1979): 2274; "Vaccination to Prevent Pneumonia," *Journal of the American Medical Association* 241 (1979): 2299. Regarding the public, see Jane E. Sisk and Richard K. Riegelman, "Cost Effectiveness of Vaccination against Pneumococcal Pneumonia: An Update," *Annals of Internal Medicine* 104 (1986): 85.

102. For a recent review of such proposals and attempts, see Mieczkowski and Wilson, "Adult Pneumococcal Vaccination," 1388–89.

103. "Trends in Morbidity and Mortality: Pneumonia, Influenza, and Acute Respiratory Conditions," American Lung Association, Best Practices and Program Services, Epidemiology and Statistics Unit, *www.lungusa.org* (accessed September 2002).

104. Of course, such a process may be altered by such contingent processes as major advances in vaccine development obvious enough to transform practice patterns in their own right.

Conclusion

1. As such, my approach has been concerned less with the status and evolution of the disease category of pneumonia per se as it has been with using the disease category as a means to examining broad therapeutic changes over time. This is not to deny, of course,

the potentially dynamic interaction between the nosologic and therapeutic approaches to disease. Indeed, chapter 2 has been explicitly concerned with such co-evolution (and the potential insights to be gained from a close examination of the history of "atypical pneumonia" as a disease concept, for example, remain to be explored).

2. As a model of general biological inquiry, the pneumococcus would be essentially ignored in the post–World War II era, eclipsed by such organisms as phage and *E.coli;* see Horace Judson, *The Eighth Day of Creation* (New York: Simon and Schuster, 1979). For the pneumococcus's parallel decline as a concern of medical research in the post–World War II era, see Maxwell Finland, "Conference on the Pneumococcus: Summary and Comments," *Reviews of Infectious Diseases* 3 (1981): 358–59; David A. Watson and David M. Musher, "A Brief History of the Pneumococcus in Biomedical Research," *Seminars in Respiratory Infections* 14 (1999): 198–208.

3. Kenneth Ludmerer, *Time to Heal: American Medical Education from the Turn of the Century to the Era of Managed Care* (New York: Oxford University Press, 1999), 26–39. Appropriately, Ludmerer does draw attention (though more cursory) to the general therapeutic advancement of the era as well.

4. Peter Keating and Alberto Cambrosio, *Biomedical Platforms: Realigning the Normal and the Pathological in Late-Twentieth-Century Medicine* (Cambridge: MIT Press, 2003), 49–82.

5. Milton Silverman and Philip Lee, *Pills, Profits, and Politics* (Berkeley: University of California Press, 1974), 1–23.

6. Harry Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (New York: Cambridge University Press, 1997), 129–63.

7. See especially Jeremy Greene's recent and cogent study of pharmaceutical marketing: "The Therapeutic Transition: Pharmaceuticals and the Marketing of Chronic Disease" (Ph.D. diss., Harvard University, 2005).

8. John Harley Warner, *The Therapeutic Perspective: Medical Practice, Knowledge, and Identity in America, 1820–1885* (Cambridge: Harvard University Press, 1986).

9. John Wennberg and Alan Gittelsohn, "Small Area Variations in Health Care Delivery," *Science* 182 (1973): 1102–8; David E. Wennberg, "Variation in the Delivery of Health Care: The Stakes are High," *Annals of Internal Medicine* 128 (1998): 866–68; John E. Wennberg and Megan M. Cooper, *The Dartmouth Atlas of Health Care in the United States* (Chicago: American Hospital Association Press, 1999).

10. Mark R. Chassin, Robert W. Galvin, and the National Roundtable on Health Care Quality, "The Urgent Need to Improve Health Care Quality," *Journal of the American Medical Association* 280 (1998): 1000–1005; Barbara J. McNeil, "Shattuck Lecture: Hidden Barriers to Improvement in the Quality of Care," *New England Journal of Medicine* 345 (2001): 1612–20; Daniel C. Silverman and Robert J. Yetman, "The Care Path Not Taken: The Paradox of Underused Proven Treatments," *Seminars in Medical Practice* 4 (2001): 6–20; Elizabeth A. McGlynn, Steven M. Asch, John Adams et al., "The Quality of Health Care Delivered to Adults in the United States," *New England Journal of Medicine* 348 (2003): 2635–45; Earl P. Steinberg, "Improving the Quality of Care—Can We Practice What We Preach?" *New England Journal of Medicine* 348 (2003): 2681–83; Claude Lenfant, "Shattuck Lecture: Clinical Research to Clinical Practice—Lost in Translation?" *New England Journal of Medicine* 349 (2003): 868–74.

11. Jerry Avorn, Milton Chen, and Robert Hartley, "Scientific Versus Commercial Sources of Influence on the Prescribing Behavior of Physicians," *American Journal of Medicine* 73 (1982): 4–8; Thomas J. Wang, John C. Ausiello, and Randall S. Stafford, "Trends in Antihypertensive Drug Advertising, 1985–1996," *Circulation* 99 (1999): 2055–57; Jerry Avorn, *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs* (New York: Alfred A. Knopf, 2004); John Abramson, *Overdosed America: The Broken Promise of American Medicine* (New York: HarperCollins, 2004).

12. Even the Institute of Medicine's report on "the urgent need to improve health care quality" missed such an opportunity in emphasizing the novelty of information overload and neglecting to mention such longstanding tensions; see Chassin, Galvin, and the National Roundtable on Health Care Quality, "The Urgent Need to Improve Health Care Quality," 1003.

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